Economics of primary caries prevention in preschool children

Yulia Anopa
BSc MSc MSc MPhil

Submitted in fulfilment of the requirements for the degree of Doctor of Philosophy

School of Medicine, Dentistry, and Nursing
College of Medical, Veterinary, and Life Sciences
University of Glasgow

December 2020

Abstract

Background: Childhood caries continues to be a pandemic disease and a significant but preventable public health problem worldwide. Caries can have a major impact on children's health and quality of life as well as represent cost to individuals, the health sector and society. Research indicates that children who develop caries in early childhood are likely to have a high risk of the disease in adolescence and adulthood. Dental caries is a preventable disease and currently a range of nationwide programmes, community-based programmes and clinical strategies exist to reduce caries prevalence in children. Notwithstanding the fact that childhood caries is very widespread and that it poses a substantial economic burden, there is a paucity of economic evaluations of caries prevention interventions in preschoolers. The lack of high-quality economic evaluations makes it difficult for decision-makers to determine which interventions to provide within the remit of health services and local authorities.

Aim: To explore the role of economic evaluation in primary caries prevention in preschool children aged 2-5 years. This aim was met through answering the following three research questions. (1) What is the existing evidence in the field of economic evaluation of primary caries prevention in children aged 2-5 years? (2) Which general health and oral health-related quality of life measures have been used in 3-5-year-old populations? And which of these measures are best suited to be used in a caries prevention randomised controlled trial for this age group? (3) Is the application of fluoride varnish delivered in nursery settings in addition to the other usual components of the Scottish child oral health improvement programme, Childsmile, (treatment as usual) cost-effective in comparison with treatment as usual only?

Methods: Three interlinked empirical work segments were undertaken to address these research questions. (1) A systematic review of economic evaluations of primary caries prevention in 2-5-year-old preschool children. (2) A non-systematic review of instruments for measuring general and oral health-related quality of life in 3-5-year-old children. (3) An economic evaluation of the

Protecting Teeth @ 3 randomised controlled trial (trial registration: EUDRACT: 2012-002287-26; ClinicalTrials.gov: NCT01674933).

Results:

(1) The systematic review of economic evaluations of primary caries prevention in 2-5-year-olds found that cost analysis and cost-effectiveness analysis were the most frequently used types of economic evaluations. Only one study employed cost-utility analysis. The systematic review highlighted wide variation in: (a) types of caries prevention interventions investigated; (b) effectiveness measures used; (c) how costs and outcomes are reported; and d) study perspective (when indicated). The parameters not reported well included study perspective, baseline year, sensitivity analysis, and discount rate. The results of the quality assessment of the full economic evaluations using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist showed substantial variation in reporting quality. The CHEERS items that were most often unmet were characterizing uncertainty, study perspective, study parameters, and estimating resources and costs.

(2) The review of general health and oral health-related quality of life measures identified a range of existing questionnaires for use in preschool populations (age 3-5 years) and their strengths and limitations were considered. Only two preference-based general health-related quality of life instruments that had been used in 3-5-year-olds were identified. No preference-based oral health-related quality of life measures for preschoolers were identified. Four instruments were selected to be used in the Protecting Teeth @ 3 trial: the Child Health Utility 9 Dimensions, PedsQL (Paediatric Quality of Life Inventory) Core, PedsQL Oral Health (an oral health specific add-on to PedsQL Core) and the Scale of Oral Health Outcomes for 5-year-old children.

(3) The findings of the Protecting Teeth @ 3 trial economic evaluation demonstrated that there were no statistically significant differences in total costs, quality adjusted life years (QALYs) accumulated, the change in the clinical effectiveness outcome (d3mft), and in general health and oral health-related quality of life measures at 24 months between the intervention and control

groups. The mean difference in total costs between the fluoride varnish (intervention) and treatment as usual (control) group was £68 (p=0.382; 95% confidence interval -£18, £144). The mean difference in QALYs was -0.004 (p= 0.636; 95% confidence interval -0.016, 0.007). The probability that the fluoride varnish intervention was cost-effective at the £20,000 threshold was 11%.

Conclusions:

The systematic review of economic evaluations of primary caries prevention in 2-5-year-olds found that within the past two decades, there has been an increase in the number of economic evaluations of caries prevention interventions in preschool children. However, there was inconsistency in how these economic evaluations of primary caries prevention were conducted and reported. Lack of use of preference-based health-related quality-of-life measures was identified. The use of appropriate study methodologies and greater attention to recommended economic evaluations design are required to further improve quality. Due to small numbers of studies investigating each intervention type (for example, fluoride varnish, oral health education, dental sealants, toothbrushing, water fluoridation) and the questionable methodological quality of many of the reviewed economic evaluations, it was not possible to arrive at reliable conclusions with regards to the economic value of primary caries prevention. With dental caries being one of the most common diseases affecting humans worldwide, the identification of cost-effective prevention strategies in children should be a global public health priority. In order for this to be achieved, studies should be designed to include economic evaluations using best practice methods guidance and adhering to standards for reporting and presenting.

The review of general health and oral health-related quality of life measures used in 3-5-year-olds identified a range of existing questionnaires for use in preschool populations – both for parental proxy reporting and child self-reporting. Four instruments were selected to be used in the Protecting Teeth @ 3 trial. Further research and development of new preference-based measures suitable for preschoolers (or their parents/guardians as a proxy) are required.

The results of the economic evaluation of the Protecting Teeth @ 3 trial show that applying fluoride varnish in nursery settings in addition to the existing treatment a usual (all other components of the Childsmile programme, apart from nursery fluoride varnish) is not likely to be cost-effective. In view of previously proven clinical effectiveness and economic worthiness of the universal nursery toothbrushing component of Childsmile, which was shown to be highly cost saving, as well as being effective and cost saving in the most deprived populations, continuation of the programme of targeted nursery fluoride varnish in its most recent (pre-COVID-19) form and shape in addition to nursery toothbrushing and other routine Childsmile components needs to be reviewed in consultation with policy makers. The findings also have wider implications for other countries looking to develop their own childhood caries prevention programmes.

Table of Contents

List of Tables

List of Figures

List of Appendices

In loving memory of

my mama Natalia (1956-1981) and papa Pavel (1952-2018)

I'm sure you would be proud of me

Acknowledgements

My PhD journey started in October 2013 and I submitted my thesis in December 2020. It took me long and sometimes painful seven years (well, minus one year of maternity leave), and my PhD labour was longer than my five-year-old daughter's life.

Over the course of this journey I worked with a lot of wonderful people who kept me going and made me a better researcher and/or person.

First and foremost, I would like to express immense gratitude to my PhD supervisors and mentors Prof Emma McIntosh and Prof Lorna Macpherson. Thank you for your support, and not only in relation to my PhD, over these years. I thank my funders the Scottish Government, for opening this opportunity to me.

My gratitude goes to all staff who worked on the Protecting Teeth @ 3 trial as well as to the trial participants. Without you this PhD would have been impossible.

I would like to thank colleagues at HEHTA: Dr Yiqiao Xin for her time, support and patience when I was getting to grips with STATA coding; Dr Jose Antonio Robles-Zurita and Robert Heggie for helping me with more STATA coding at a time of utter desperation; Dr Nicole Boyer for being an example and an inspiration for starting my work in the field of economic evaluation of child public health interventions; I would like to thank fellow students in the HEHTA's PhD room for the chats that kept my spirits up.

My thanks go to colleagues and friends at the COH office at the Dental School. Namely, to John McHugh, Jessica Brewster, and Isla McCormick for their assistance with administration and record keeping for the PT@3 trial, to Pauline Daniel for the overall administrative support, and to everybody else in the office and in the PhD room.

Thank you to the Childsmile Regional Research Team members (past and present) for your help and comradery over the years, including Dr Leigh Deas, Jennifer Eaves and Nicola Williams.

Thank you to Paul Cannon for his help and valuable advice with the literature searching.

I would like to thank Prof Olivia Woo and Prof David Conway for being my annual PhD progress meeting panel members over the years and for their insights on the ways to improve my research.

On a personal note, I express my deep and sincere gratitude to my family for their continuous and unparalleled love, help and support. I must thank my husband Andrew for supporting me through all highs and lows: without you I would not have managed it. I thank our daughter Lia for being my muse, for smiles and for sharing fun times and adventures with me.

And, last but not least, I would like to thank me for not giving up and seeing it through to the end.

Author's Declaration

I declare that, except where explicit reference is made to the contribution of others, the thesis is my own composition and has not been submitted in part or whole for any other degree.

Yulia Anopa

Glasgow - December 2020

Publications and Presentations

Parts of the research work included in this thesis have been published and/or presented in international and national conferences.

Publications:

Anopa Y, Macpherson L, McIntosh E. Systematic Review of Economic Evaluations of Primary Caries Prevention in 2- to 5-Year-Old Preschool Children. Value in Health. 2020.

The thesis author / paper was awarded the 2020 Yorkhill Prize for Postgraduate Research (prizes are awarded annually for excellence in the area of paediatrics), £250 - one of four equal prizes (https://www.gla.ac.uk/schools/medicine/research/childhealth/childhealthprizes/).

International conferences:

Anopa, Y., Macpherson, L. M., & McIntosh, E. Economic evaluations of primary caries prevention in 2-5-year-old preschool children: a systematic review. European Association of Dental Public Health conference, 18-20 October 2018, Palma de Mallorca, Spain (poster and short oral presentation).

Anopa, Y., Macpherson, L. M., & McIntosh, E. Economic evaluation of the Protecting Teeth @ 3 randomised controlled trial. European Association of Dental Public Health (EADPH) conference, 12-14 September 2019, Ghent, Belgium (pre-selected for oral presentation).

The thesis author was competing with three other pre-selected oral presenters for the EADPH GlaxoSmithKline Research Award. The presentation was awarded the first prize (€2,000).

[Published abstract] Anopa, Y., Macpherson, L. M., & McIntosh, E. (2019). Economic evaluation of fluoride varnish application of daily supervision versus daily supervision and additional six-monthly intervals in Scotland (Protecting

Teeth@ 3): A randomised controlled trial. The Lancet, 394, S18. (DOI: https://doi.org/10.1016/S0140-6736(19)32815-6). The Lancet Public Health Science conference, 29 November 2019, London, UK (poster).

National conferences:

Anopa, Y. Economic evaluation of the Protecting Teeth @ 3 randomised controlled trial. Scottish Oral Health Research Collaboration (SOHRC) Conference 2019, 1 October 2019, Dundee, UK (3-minute oral presentation).

Abbreviations

A&E	Accident and Emergency
ACER	average cost-effectiveness ratio
aOR	adjusted odds ratio
CADTH	Canadian Agency for Drugs and Technologies in Health
CARIES-QC	Caries Impacts and Experiences Questionnaire for Children
CBA	cost-benefit analysis
CCA	cost-consequence analysis
CEA	cost-effectiveness analysis
CEAC	cost-effectiveness acceptability curve
CHEERS	Consolidated Health Economic Evaluation Reporting Standards
CHU9D	Child Health Utility 9 Dimensions
CI	confidence interval
CMA	cost-minimisation analysis
CUA	cost-utility analysis
DALY	disability-adjusted life year
DHSW	dental health support worker
ECC	early childhood caries
ECOHIS	Early Child Oral Health Impact Scale
EE	economic evaluation
EQ-5D	EuroQol 5 Dimensions
FS II-R	Functional Status II(R)
FV	fluoride varnish
FVA	fluoride varnish application
GA	general anaesthesia
GHQoL	general health-related quality of life
GP	general practitioner
HEHTA	Health Economics and Health Technology Assessment
HRQoL	health-related quality of life
HSCS-PS	Health Status Classification System Preschool
HTA	Health Technology Assessment
HUI	Health Utilities Index
ICER	incremental cost-effectiveness ratio

ICOHIRP	International Centre for Oral Health Inequalities Research & Policy
ISPOR	International Society for Pharmacoeconomics and Outcomes Research
ITQOL	Infant Toddler Quality of Life Questionnaire
IVRS	Interactive Voice Response System
MAR	missing at random
MCAR	missing completely at random
MNAR	missing not at random
NDIP	National Dental Inspection Programme
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
NNT	number needed to treat
OECD	Organisation for Economic Co-operation and Development
OH	oral health
OHQoL	oral health-related quality of life
OR	odds ratio
PedsQL	Paediatric Quality of Life Inventory
PedsQL-OH	Paediatric Quality of Life Inventory Oral Health Scale
PHI	public health intervention
PICOS	Participants, Interventions, Comparators, Outcomes, and Study design
POQL	Paediatric Oral Health-Related Quality of Life
PRISMA	Preferred Reporting System for Systematic Reviews and Meta-Analysis
PSSRU	Personal Social Services Resource Unit
PT@3	Protecting Teeth at 3 trial
QALY	quality adjusted life year
QWB	Quality of Well-Being Scale
RCT	randomised controlled trial
ROI	return on investment
SD	standard deviation
SF-12	Short Form 12
SF-36	Short Form 36
SF-6D	Short Form 6 Dimensions
SF-6D	Short Form 6 Dimensions
SG	standard gamble

SIMD	Scottish Index of Multiple Deprivation
SOHO-5	Scale of Oral Health Outcomes for 5-year-old children
TAPQOL	TNO-AZL Questionnaire for Preschool Children's Health-Related Quality of Life
TAU	treatment as usual
TTO	time trade-off
UK	United Kingdom
WCHMP	Warwick Child Health and Morbidity Profile
WHO	World Health Organization

Chapter 1 Introduction

1.1 Introduction to Chapter 1

Untreated dental caries is one of the most common diseases affecting humans worldwide (Frencken et al. 2017, Peres et al. 2019) and it is the most widespread non-communicable disease (WHO 2017b). The global epidemiology of early childhood caries has demonstrated the prevalence of caries in preschool children in both developed and developing countries (WHO 2017b). In 2010, untreated caries in deciduous teeth was the tenth most prevalent health condition, affecting 9% of the global child population; the global age-standardised prevalence remained unchanged between 1990 and 2010 (9%) (Marcenes et al. 2013, Peres et al. 2019). In 2015, untreated caries in deciduous teeth affected 573 million children worldwide, and accounted for approximately 100,000 disability adjusted life years (DALYs) (Kassebaum et al. 2017).

Oral conditions and diseases, including caries, disproportionally affect more impoverished and socially disadvantaged members of society (Peres et al. 2019). There is a strong and consistent social gradient between socioeconomic status and the prevalence and severity of oral diseases. Oral diseases can be considered as a sensitive clinical marker of social disadvantage, being an early indicator of population ill health linked to deprivation. Oral health inequalities are directly influenced by wider social and commercial determinants, which are the underlying drivers of poor population oral health (Peres et al. 2019).

The high prevalence of caries in preschool children worldwide has a major impact on children's health as well as cost to society (Tinanoff et al. 2019). Caries can lead to pain, infections, difficulties with eating, sleeping and socialising, and poor school performance (ICOHIRP 2015, White 2017, Phantumvanit et al. 2018, Tinanoff et al. 2019). Caries can also lead to hospitalizations and emergency room visits, and delays of growth and development (Tinanoff et al. 2019). Children with caries in their primary teeth are five times more likely to develop caries in their permanent teeth than children without primary teeth caries (Hall-Scullin et al. 2017). Preschool

children with active caries were found to have higher incidence rates for pain and extractions in primary molar teeth (Tickle et al. 2008).

Childhood caries poses an economic burden to individuals, the health sector and society (Phantumvanit et al. 2018). Untreated caries was found to cause 12% of global productivity losses due to dental diseases in 2015: $21.19 billion (11%) due to untreated caries in permanent teeth, and $0.90 billion (0.5%) to caries in deciduous teeth (Righolt et al. 2018).

Notwithstanding the fact that childhood caries is widespread and that it poses a substantial economic burden, there is a paucity of economic evaluations of caries prevention interventions in preschoolers. Previously published reviews of economic evaluations of oral health interventions (Kallestal et al. 2003, Coffin et al. 2013, Marino et al. 2013, York Health Economics Consortium 2016e, Hettiarachchi et al. 2018, Rogers et al. 2019) identified only a small number of studies conducted in preschool populations. Therefore, there is currently a mismatch between the significant burden of early childhood caries, including economical burden, and the small amount of published research on the cost-effectiveness of caries prevention interventions in younger children.

Chapter 1 firstly covers some generic dental aspects, such as the definitions of caries and early childhood caries (ECC), aetiology and measurement of caries, epidemiology and inequalities in ECC, caries risk factors, impacts of ECC, and prevention of ECC (Sections 1.2 to 1.7). Further on, this chapter outlines some economics-related aspects: Section 1.8 introduces economics of early years interventions in general, while Section 1.9 discussed economics of ECC in particular. Section 1.11 introduces Childsmile - a national programme in Scotland designed to improve the oral health of children and reduce inequalities both in dental health and access to dental services (Childsmile 2020b), as well as the Protecting Teeth @ 3 randomised controlled trial, which was conducted within Childsmile. Finally, Section 1.12 describes the current situation with regard to economic evaluations in child caries prevention.

This chapter also presents the aims and objectives of this thesis (Section 1.13) and outlines the overall thesis structure (Section 1.14).

1.2 Dental caries

1.2.1 Definition and aetiology of dental caries

Dental caries is a biofilm-mediated, diet modulated, multifactorial, non-communicable, dynamic disease resulting in mineral loss of dental hard tissues (Fejerskov 1997, Pitts et al. 2017). As a consequence of this process, a caries lesion develops. Caries is determined by biological, behavioural, psychosocial, and environmental factors (Machiulskiene et al. 2020). In simpler terms, dental caries is defined as the "chemical dissolution of a tooth surface brought about by metabolic activity" in a dental biofilm (also called dental plaque), which covers a tooth surface (Kidd and Fejerskov 2016). Dietary sugars are metabolised by bacteria in the dental plaque biofilm to produce acids which cause dissolution of the tooth surface through mineral loss. The presence of fluoride in the saliva and in the biofilm also plays a major role, as well as other salivary and genetic factors (Pitts et al. 2017).

Dental caries results from the interaction of various aetiological factors, which might be concurrently present to initiate and progress the disease. The factors are: 1) cariogenic microorganisms; 2) fermentable carbohydrates (substrate), such as the presence of high levels of free sugars; 3) levels of exposure to fluoride; 4) susceptible tooth surface/host; and 5) saliva composition (Anil and Anand 2017, Macpherson et al. 2019a). Figure 1.1 shows the interactions of these factors in the aetiology of caries.

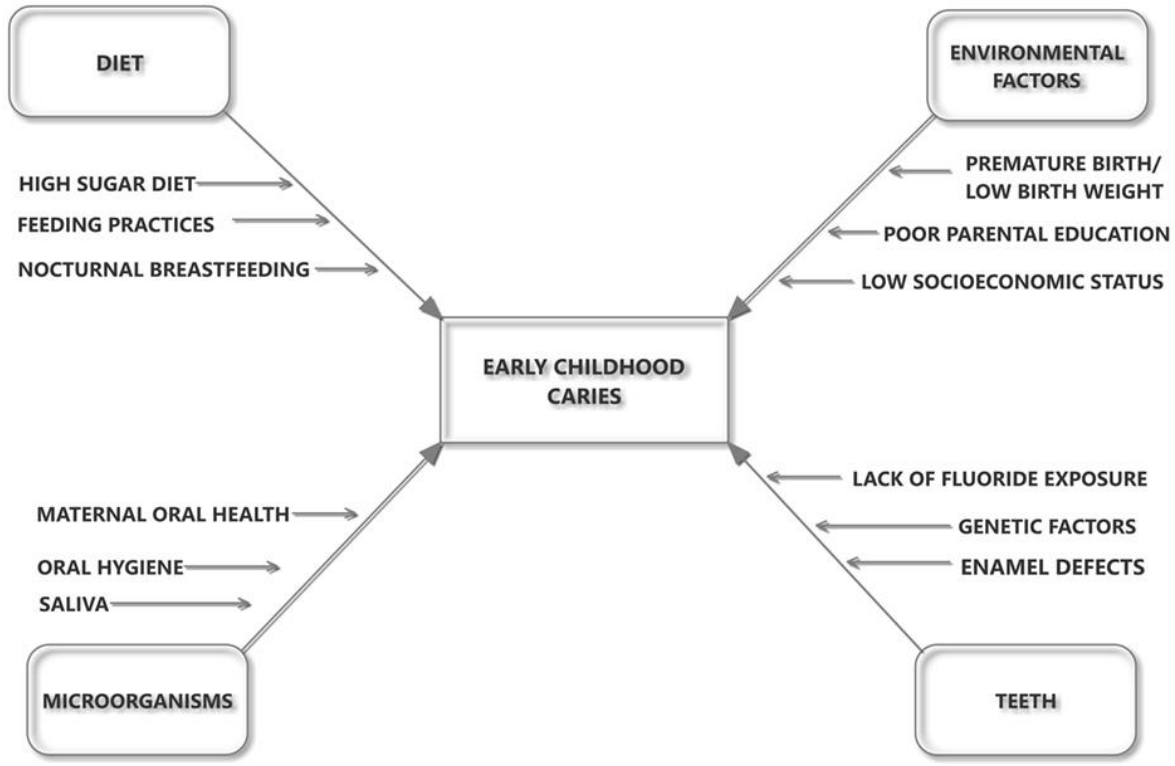

Figure 1.1 The influence of host-microbe-diet interactions in the aetiology and pathogenesis of caries

Source (Anil and Anand 2017).

The dynamic caries process consists of rapidly alternating periods of tooth demineralisation and remineralisation (Pitts et al. 2017). Under normal conditions, there is an equilibrium of alternating period of demineralisation and remineralisation during the day in individuals' mouths. Demineralisation follows consumption of free sugars which are metabolised to form acids. Higher level of acids can lead to low pH and dissolution of the tooth structure. Certain properties of saliva (such as higher flow rate and buffering capacity) and presence of fluoride in the mouth tend to stop the demineralisation process and can lead to remineralisation (Fejerskov et al. 2015). On the other hand, if exposure to free sugars is frequent, the pH will remain low for prolonged periods of time, and the balance can be tipped in favour of demineralisation with subsequent caries development (Tinanoff et al. 2019). Fluoride has a major role in influencing the process and can have a topical caries-reduction effect. However, for this to occur, fluoride should be present in the oral fluids at slightly elevated levels for prolonged periods during the day (Fejerskov et al. 2015). If net demineralisation occurs over sufficient time caries lesions develop. Thus, it is important to balance the pathological and protective factors which

influence the initiation and progression of caries. Protective factors promote remineralisation and lesion arrest, whereas pathological factors, on the contrary, shift the balance in the direction of dental caries and disease progression (Figure 1.2) (Pitts et al. 2017).

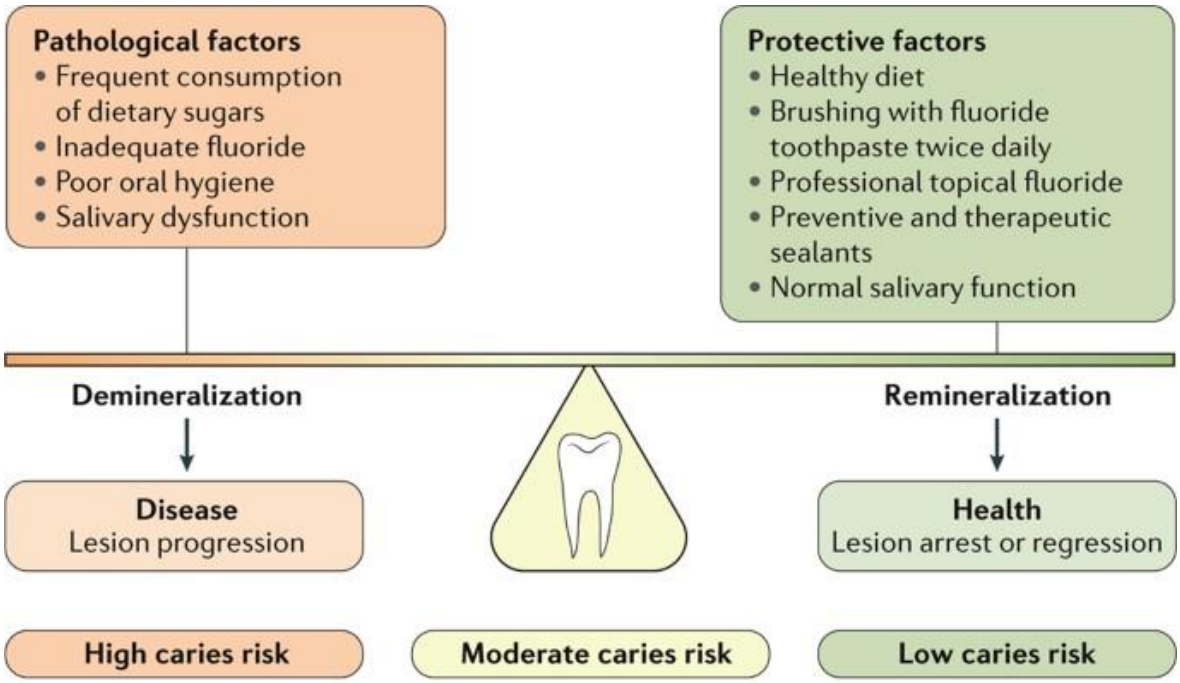

Figure 1.2 Balancing pathological and protective factors in dental caries

A focus on optimising the protective factors (those favouring healthy teeth) promotes remineralisation and shifts the dynamic balance of the caries process in the direction of health and lesion arrest.

Source (Pitts et al. 2017).

1.2.2 Measurement of dental caries

In dental epidemiology, dental caries is usually recorded at the caries into dentine level (dentinal caries) (Conway et al. 2014). Dentinal caries lesions are recorded following visual clinical inspection, which involves examination with the naked eye under standard lighting, without the use of a dental probe or radiographs (Ismail 2004). Due to the possibility of subclinical (not visually obvious decay) being present, the term “no obvious decay experience” has been more widely used in recent years instead of the traditional term “caries free” (Selwitz et al. 2007, Conway et al. 2014). The various thresholds of dental caries diagnosis are shown in Figure 1.3.

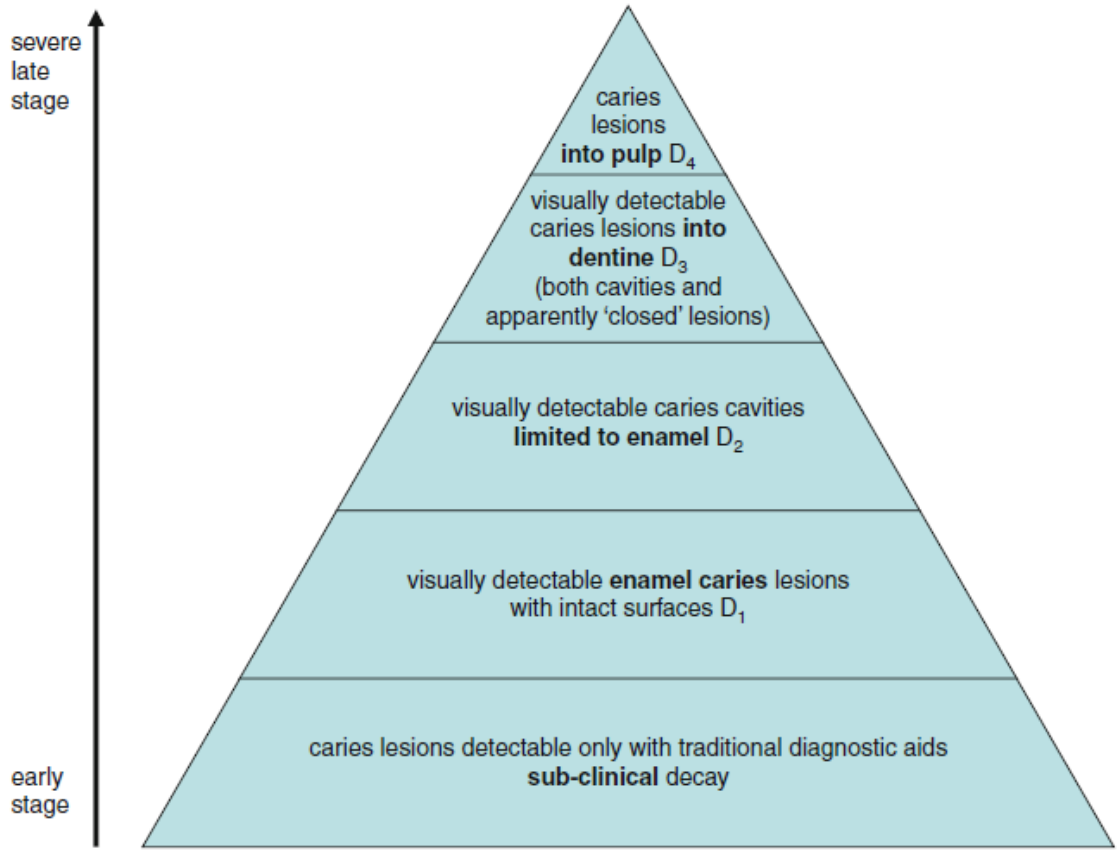

Figure 1.3 Pyramid of thresholds of dental decay

Adapted from (Pitts 2001).

The traditional global index used to measure caries in epidemiological studies is the D3MF/d3mf index (Conway et al. 2014, Pitts et al. 2017). Upper case letters (DMF) are used for the permanent dentition, while lower case (dmf) is used for deciduous teeth (baby teeth). The subscript "3" indicates caries at the level into dentine. The D3MF/d3mf index is the sum of the number of decayed, missing due to decay, or filled teeth (D3MFT/d3mft) or decayed, missing, or filled (tooth) surfaces D3MFS/d3mfs (Conway et al. 2014).

1.2.3 Early childhood caries

Early childhood caries (ECC) is defined as the presence of one or more decayed, missing, or filled tooth surfaces in any primary tooth in a child at 71 months of age or younger (under 6 years of age) (Drury et al. 1999, Anil and Anand 2017). More precise case definitions of ECC and severe ECC are shown in Table 1.1. Historically, ECC was labelled as comforter caries, baby bottle tooth decay, nursing caries, nursing bottle / baby bottle syndrome, nursing bottle caries, prolonged nursing habit caries or rampant caries (Ismail 2003, Anil and Anand

2017, Tinanoff et al. 2019). The current term ECC implies a more complex disease, related to frequent sugar consumption in the environment of enamel-adherent bacteria that is not necessarily related to bottle feeding (Tinanoff et al. 2019).

Table 1.1 Case definitions of early childhood caries and severe early childhood caries

Age (Months)	Early childhood caries criteria	Severe early childhood caries criteria
<12	1 or more dmf surface *	1 or more smooth dmf surfaces
12-23	1 or more dmf surface *	1 or more smooth dmf surfaces
24-35	1 or more dmf surface *	1 or more smooth dmf surfaces
36-47	1 or more dmf surface *	1 or more cavitated, filled, or missing (due to caries) smooth surfaces in primary maxillary anterior teeth OR dmfs score ≥4
48-59	1 or more dmf surface *	1 or more cavitated, filled, or missing (due to caries) smooth surfaces in primary maxillary anterior teeth OR dmfs score ≥5
60-71	1 or more dmf surface *	1 or more cavitated, filled, or missing (due to caries) smooth surfaces in primary maxillary anterior teeth OR dmfs score ≥6

Notes: * Any carious lesion, non-cavitated (d1) or cavitated (d2, d3), missing tooth due to caries (m), or filled surface (f). Includes primary teeth only.
Adapted from (Drury et al. 1999).

ECC continues to be a pandemic disease worldwide (WHO 2017b). ECC progresses more rapidly than caries in the permanent dentition due to the morphology of the teeth (Phantumvanit et al. 2018, Schmoeckel et al. 2020). ECC can be a particularly virulent form of caries, beginning soon after dental eruption, developing on smooth surfaces, progressing rapidly, and having a lasting detrimental impact on the dentition (Colak et al. 2013).

ECC is a public health problem, with greatest severity in communities of low socioeconomic status where untreated caries have a major impact on the general health and quality of life of infants, toddlers and preschoolers (WHO 2017b). Structural factors and poor socioeconomic conditions have an important impact on the development of ECC and lead to inequalities in caries experience distribution (Phantumvanit et al. 2018). Caries prevalence and severity disparities also exist across certain racial/ethnic groups in society, reflecting socioeconomic disadvantage and cultural differences (Watt et al. 2018).

1.3 Epidemiology of dental caries in children

Representative international data on ECC is sparse, as most countries only report caries from age 5 or 6 years (Pitts et al. 2017). The most recent findings from the WHO database on dental caries epidemiology revealed that the medians of mean d3mft scores (cavitated dentine carious lesions) in 5- and 6-year-olds were as follows: 2.0 in the high-income group, 3.9 in the upper-middle-, 4.1 in lower-middle-income group and 4.4 in the low income group (the last group included data only for three countries) (Frencken et al. 2017).

One study summarised trends in the dental health of children in the UK over 40 years from 1973 to 2013 (Murray et al. 2015) and found that in 1973 the mean dmft of 5-year-olds was 4.0, while in 2013 the mean dmft was 0.9, and 31% of 5-year-olds had obvious caries experience. Neither the 1973 nor 2013 survey data, however, included Scottish data. Table 1.2 shows the proportions of children with obvious decay, mean dft (number of decayed, into dentine, and filled deciduous teeth) for the overall sample and mean dft for children with obvious decay (those with dft>0). The data indicate that all three indicators gradually decreased over time.

Table 1.2 Caries experience (obvious decay into dentine) in 5-year-old children in England and Wales (1973), UK (1983, 1993 and 2003) and England, Wales and Northern Ireland (2013)

	1973	1983	1993	2003	2013
Percent with obvious decay (children with dft>0)	72%	52%	46%	43%	26%
Mean dft	4	1.8	1.7	1.6	0.7
Mean dft in children with obvious decay (dft>0)	5.5	3.5	3.7	3.5	2.8

Notes: 1) dft – number of decayed (into dentine) and filled deciduous teeth. 2) There were changes in geographic survey coverage and consent methodology between 2003 and 2013.

Source (Murray et al. 2015).

Historically, Scottish children suffered poor oral health. In 1983, only 24% of five-year-olds in Scotland had no obvious caries experience (Pitts and Davies 1988). By 1988, there had been a substantial decrease in caries prevalence with 42% of five-year-olds having no obvious caries experience (Merrett et al. 2006) associated with the increased use of fluoridated toothpaste. This rose slightly to 45% in the 2003 inspection but the overall trend in improvement had plateaued

(Scottish Dental Epidemiological Co-ordinating Committee 2003). According to epidemiological surveys at the beginning of the 21st century, children in Scotland (as well as Northern Irish children) had the worst oral health in the United Kingdom and among the worst in Europe, comparable with Eastern European countries (Scottish Dental Epidemiological Co-ordinating Committee 2003). The figures below illustrate changes in 5-year-olds' oral health over time (NDIP 2020). Figure 1.4 shows trends in the proportion of 5-year-olds with no obvious decay experience. There was a flat trend between 1988 and 2003 (the change over this period was from 42% to 45%), while from 2004 onwards there has been a steady increase in the proportion of children without obvious decay. In 2020, 74% of children had no obvious decay. Figure 1.5 shows the mean d3mft over time. Similarly, there has been a substantial decrease in 5-year-olds' d3mft (improvement in oral health) from 2.76 in 2003 to 1.04 in 2020.

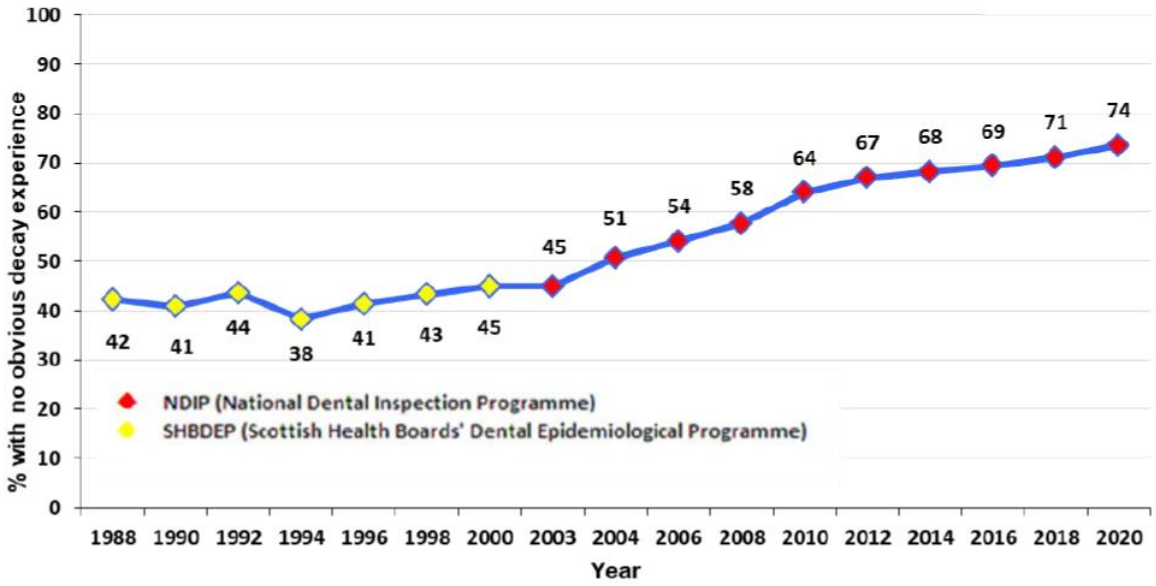

Figure 1.4 Trends in the proportion of 5-year-old children with no obvious decay experience in Scotland, 1988-2018

Notes: 1) No obvious decay experience is when d3mft=0; 2) The distance between each point does not represent an equal period of time as the results have not been published consistently over the 30-year period. Source (NDIP 2020).

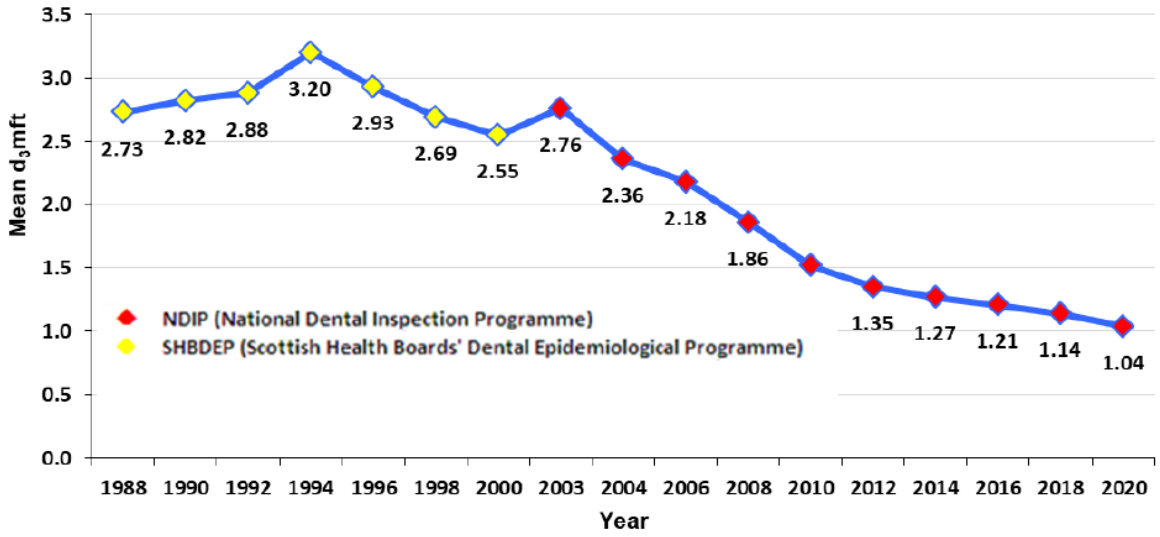

Figure 1.5 Mean number of decayed, missing and filled primary teeth (d3mft) in the 5-year-old population in Scotland, 1988-2020

Note: The distance between each point does not represent an equal period of time as the results have not been published consistently over the years. Source (NDIP 2020).

1.4 Inequalities in early childhood caries

ECC is more prevalent among the more socially disadvantaged groups in both developing and industrialized countries (Edelstein 2006, Anil and Anand 2017). This could be related to low socioeconomic status, social exclusion, and sociocultural differences in oral health beliefs and practices (Edelstein 2009).

Oral health (and ECC) disparities are not merely the differences between the rich and poor in society. A consistent, stepwise, graded relationship exists across the entire social spectrum, with oral health being worse at each point down the social hierarchy, which is called the social gradient (Watt 2012, Watt et al. 2018). Oral health disparities also exist across certain racial/ethnic, reflecting socioeconomic disadvantage and cultural differences (Watt et al. 2018). Effective action to tackle oral health inequalities can only be developed when the underlying causes of the problem are identified and understood (Watt 2007).

One of the goals of the detailed dental inspection conducted by the National Dental Inspection Programme (NDIP) in Scotland is to determine the influence of deprivation on the dental health of children (NDIP 2020). NDIP uses the Scottish Index of Multiple deprivation (SIMD) classification based on quintiles of deprivation, where quintile SIMD 1 is the most deprived and quintile SIMD 5 is

the least deprived (Scottish Government 2016b). Figure 1.6 shows the change between 2012 and 2020 in the percentage of 5-year-old children in Scotland with no obvious decay experience (d3mft=0) by SIMD quintile, according to a recent NDIP report (NDIP 2020). The figure illustrates that although there was an improvement in child dental health overtime within each of the deprivation quintiles, the proportions of children with no obvious decay experience were considerably lower in the more deprived quintiles. There is a clear social gradient in caries prevalence. In the period 2012-2020, the proportion of children with no obvious decay in SIMD1 increased from 51% to 58%, whereas the improvement in SIMD5 was from 81% to 87%. The absolute inequality between SIMD 1 and SIMD 5 (proportion of children with no obvious decay in SIMD5 minus proportion of children with no obvious decay in SIMD1) remained around 30% over time, with only small fluctuations either side of this figure.

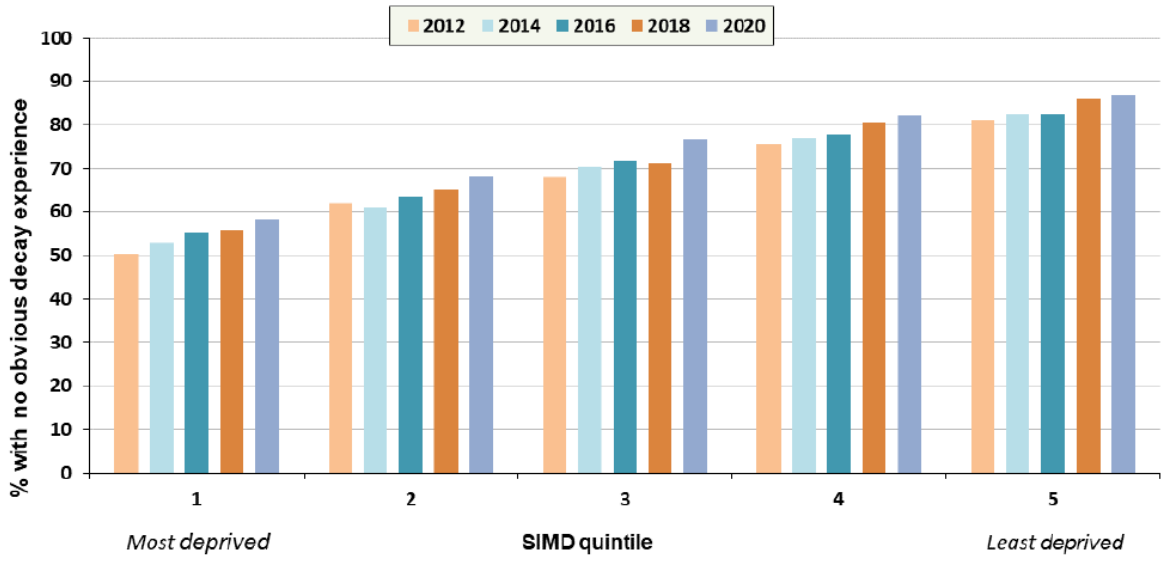

Figure 1.6 Change between 2012 and 2020 in the percentage of 5-year-old children in Scotland with no obvious decay experience; by SIMD quintile.

Notes: SIMD1 is most deprived, SIMD5 is least deprived quintile. No obvious decay experience is when d3mft=0. Source (NDIP 2020).

According to the National Dental Epidemiology Programme for England 2015 report, inequalities were also found according to ethnicity with 51% of Chinese 5-year-olds having obvious decay, followed by 48% of Eastern European, and with the remaining ethnical groups ranging from 45% to 21% (Public Health England 2016a, Godson et al. 2018).

1.5 Caries risk factors

Caries is known to be a multifactorial disease (Meyer and Enax 2018). A recent systematic review and meta-analysis of case-control and cohort studies on risk factors for ECC (Kirthiga et al. 2019) identified 89 studies and found 123 individual risk factors. These individual factors were grouped into seven categories: factors related to diet (28 factors), breastfeeding factors (10), bottle feeding factors (15), oral hygiene habits factors (10), factors related to oral bacteria (3), sociodemographic factors (19), and related to other factors (38). The meta-analysis conducted by Kirthiga and colleagues showed that the important risk factors, namely, those with odds ratio (OR) greater than one, in high income countries were: low maternal education; low birth weight (less than 2,500 g); smoking during pregnancy; the presence of mutans streptococci (cariogenic oral bacteria); increased daily sweetened fizzy drinks intake; maternal age younger than 25 years; visible plaque present; bad oral hygiene; night bottle feeding; liquids other than milk in bottles; the presence of lactobacilli (cariogenic oral bacteria); tooth brushing less than once daily; age when brushing began at one year of age or older; negative parental attitudes; frequent consumption of sweetened foods; daily intake of sugary snacks; and intake of sugary beverages. The strongest risk factors were: high levels of mutans streptococci (OR = 3.83 [1.81 to 8.09]); frequent consumption of sweetened foods (OR = 3.14 [0.89 to 11.04]); poor oral hygiene (OR = 3.12 [1.77 to 5.49]); and visible plaque present (OR = 3.10 [2.0 to 4.80]) (Kirthiga et al. 2019).

According to WHO, the two major reasons for the burden of dental caries relate to the high consumption of sugars and inadequate exposure to fluoride (Petersen and Ogawa 2016). Caries is not the result of fluoride deficiency, however, the fluoride ion can have a major caries-reduction effect on biofilm-covered tooth surfaces in the oral cavity (Fejerskov et al. 2015). Fluoride in toothpaste is considered a main contributor to the decline in dental caries (Petersen and Ogawa 2016). However, fluoridated toothpastes are not universally used due to the cost factor associated with buying the toothpaste, which inhibits poor population groups from accessing this preventive measure. Toothbrushing with non-fluoride toothpaste (Walsh et al. 2019), late commencement of child

toothbrushing, irregular toothbrushing, not having teeth brushed at bedtime and toothbrushing without supervision by a caregiver (Anil and Anand 2017, Meyer and Enax 2018, Kirthiga et al. 2019) are important factors that increase the risk of developing ECC.

There are also other risk factors of ECC. Enamel hypoplasia (a defect of the enamel that only occurs while teeth are still developing) significantly increases the risk of developing caries (Kirthiga et al. 2019). Low birth weight and preterm birth have also been found to be associated with ECC (Anil and Anand 2017). A recent systematic review and meta-analysis indicated a significantly higher prevalence of early childhood caries in children born moderate to late preterm compared to full term children (Twetman et al. 2020).

Oral diseases disproportionately affect socially disadvantaged groups in society (Watt et al. 2018). Low socioeconomic status, unemployment and migration background are well-known risk factors for ECC (Anil and Anand 2017, Meyer and Enax 2018). Children from poorer backgrounds have higher rates of caries and often experience dental pain and its consequences (Watt et al. 2018).

Oral diseases and oral health inequalities are directly influenced by wider social and commercial determinants, which are the underlying drivers of poor population oral health (Peres et al. 2019). More often than not, people's choices, detrimental to their health, are structured by bigger forces outside their own control (McKee and Stuckler 2018). Families living in disadvantaged communities have limited choices available to them, and their daily lives are a constant struggle to do the best they can for their children. Oral health-related behaviours (such as high sugar and high carbohydrate diets, or inadequate oral hygiene and lack of fluoride in toothpaste) are important influences on their oral health, however, these behaviours are largely determined by the social and physical conditions in which people live (Watt et al. 2018). Families and individuals might not have full control over their oral health if they have insufficient funds to purchase beneficial goods and healthy foods (Birch and Listl 2015, Peres et al. 2019).

In their 2016 paper, Kickbusch and colleagues defined the commercial determinants of health as *"strategies and approaches used by the private sector to promote products and choices that are detrimental to health"* (Kickbusch et al. 2016). This definition includes consumer and health behaviour, individualisation, and choice (at the micro level); and the global risk society, the global consumer society, and the political economy of globalisation (at the macro level). The global sugar industry provides a sharp example of commercial determinants of health, with sugary soft drinks and added sugar in processed food being major sources of sugar in the global diet (Peres et al. 2019).

A conceptual framework of combined social and commercial determinants of oral health is presented in Figure 1.7 (Peres et al. 2019). It highlights the interacting influences and processes.

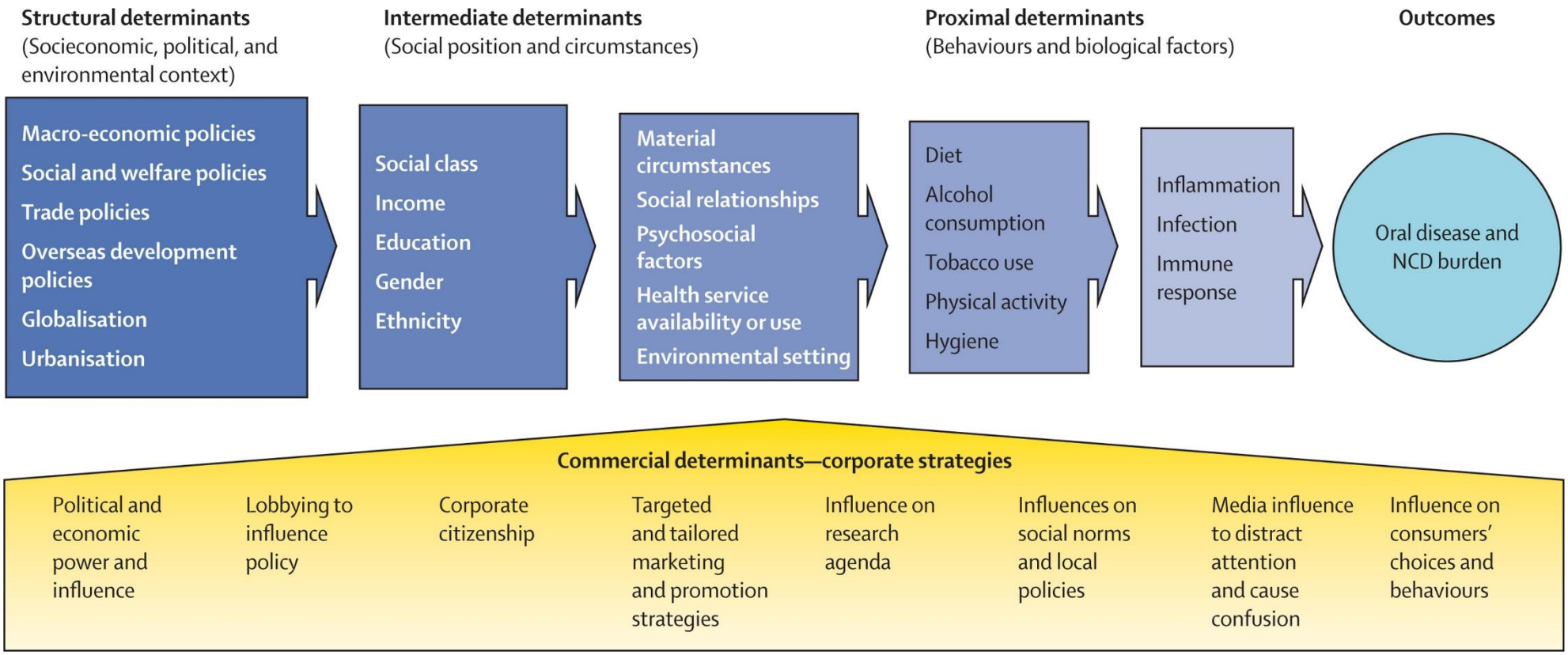

Figure 1.7 Social and commercial determinants of oral diseases

NCD – non-communicable disease. Source: (Peres et al. 2019), adapted from (Watt and Sheiham 2012).

1.6 Impacts of early childhood caries

The high prevalence of caries in children under six years of age worldwide has a major impact on children's health as well as cost to society (Tinanoff et al. 2019). Although a highly prevalent condition, the impact of childhood dental caries is often underappreciated as the disease is rarely life-threatening or overtly limiting on daily activities (Innes and Robertson 2018). Nevertheless, it carries significant consequences for children in terms of day-to-day living and is expensive to treat. ECC can lead to pain, infections, impaired chewing and difficulties with eating, sleeping, socialising, and poor school performance thus affecting a child's general health and child and family quality of life (ICOHIRP 2015, White 2017, Phantumvanit et al. 2018, Tinanoff et al. 2019). Consequences of ECC also include hospitalizations and emergency room visits, and delays of growth and development (Tinanoff et al. 2019). Early extractions of primary teeth due to ECC may lead to malocclusions (Seow 2018). It often leads to school absenteeism and parents taking time off work to take their children to a dentist or to hospital (York Health Economics Consortium 2016e, White 2017). Poor oral health of a child may be a sentinel marker of wider health and social issues, and dental neglect may be part of a safeguarding issue (Harris et al. 2009, Harris et al. 2013, Godson et al. 2018).

Children with a pre-existing caries lesion have a 5–6 times higher incidence of developing new caries lesions compared to previously caries-free children (Milsom et al. 2008). Research indicates that children who develop caries in early childhood are likely to have a high risk of the disease in adolescence and adulthood, in permanent teeth (Li and Wang 2002, Anil and Anand 2017, Hall-Scullin et al. 2017, Seow 2018, Tinanoff et al. 2019). A Chinese eight-year cohort study with children aged 3-5 years at baseline (Li and Wang 2002) found statistically significant associations between caries prevalence in primary and permanent dentitions. Children who had caries in their primary teeth were three times more likely to develop caries in their permanent teeth (relative ratio was 2.6, 95% CI 1.4-4.7; $p < 0.001$), with caries on primary molars having the highest predictive value (85.4%).

A recent UK longitudinal cohort study followed over 6,600 children aged 7–9 years at baseline for three years (Hall-Scullin et al. 2017). The children underwent a dental examination each year (there were four dental examinations in total, including the baseline). The children attended 207 state-funded primary schools in East Lancashire in the northwest of England. The location was chosen for its comparatively high caries prevalence and the absence of a fluoridated water programme. The results of the study indicated that mean caries prevalence in the permanent dentition (% D3MFT > 0) was 17% at the first clinical examination (ages 7–9 years), increasing to 31%, 42%, and 46% at subsequent examinations. A population-averaged model (generalized estimating equations) was used to model the longitudinal data. Children with caries in their primary teeth were almost five times more likely (4.49 times; 95% CI 3.90–5.16) to develop caries in their permanent teeth than children whose primary dentition was caries free. The results of the study showed that deprivation remained an important predictor of future caries and that children who have caries in their primary dentition followed a steep disease development trajectory in their permanent dentition. These findings illustrate the significant long-term consequences of developing caries in early childhood.

Preschool children with active caries were found to have higher incidence rates for pain and extractions in primary molar teeth. A prospective three-year UK-based cohort study followed children aged 3 to 6 years attending 50 dental practices in the North West of England (Tickle et al. 2008). Incidence rates for pain and extractions in primary molar teeth were calculated for children with and without dental caries. Each year approximately one in five children with active caries presented with dental pain at an unscheduled visit at the dentist, compared with only 1 in 100 children who were caries free. Having caries in primary molar teeth at an early age was also a strong risk factor for future dental extractions: 26% of children with caries at baseline had extractions compared to 3% in those who were caries-free at baseline. In children with active caries, 1 in 10 had a primary molar tooth extracted each year, compared with 1 in 40 in the whole population.

1.7 Prevention of early childhood caries

To manage ECC rationally, strategies must focus on the right causes at the right time and should focus on preventing initiation rather than on controlling severity (WHO 2017b). In order to prevent or control caries, from a biological perspective, sugar and biofilm control is required, as well as ensuring fluoride bioavailability (Macpherson et al. 2019a).

There is a strong economic case for investing in noncommunicable disease prevention (WHO 2015). The main risk factors associated with noncommunicable diseases, including caries, are largely preventable and addressing those risk factors can be an efficient use of governments' money. Upstream prevention investment, prior to the onset of illness and before health care services are required, seems to be most cost-effective (WHO 2015). Upstream, midstream and downstream approaches to ECC prevention are described in Section 1.7.3.

1.7.1 Primary, secondary and tertiary prevention

Prevention of ECC can be classified into three levels: primary prevention, secondary prevention and tertiary prevention (FDI World Dental Federation 2016, WHO 2017b). Primary prevention of ECC needs to begin before the initiation of disease and is the key to reducing the worldwide prevalence of ECC (Tinanoff et al. 2019). It is most effective when exposure to disease causes is controlled, by modifying unhealthy behaviours and increasing resistance to the disease (FDI World Dental Federation 2016). It includes promotion of healthy behaviours and appropriate fluoride use (WHO 2017b). Secondary prevention occurs in the early stages of caries and aims to reduce its impact as early as possible. It is carried out through early detection and prompt care in order to halt, slow or reverse caries progression (FDI World Dental Federation 2016). Tertiary prevention of ECC occurs in later stages of caries and aims to reduce the negative impact of the untreated open cavity and improve or sustain children's ability to function and their quality of life, while continuing to prevent new lesions (FDI World Dental Federation 2016, WHO 2017b).

At all three levels, prevention is a shared responsibility of individuals, dental professionals and the community at large (FDI World Dental Federation 2016).

This is particularly true for primary caries prevention. Since caries is largely preventable, the earlier the prevention is done, the more likely it is that the intervention will be effective. Table 1.3 illustrates the different responsibilities that individuals, oral health professionals and the community share in primary, secondary and tertiary prevention.

Table 1.3 Responsibilities of individuals, oral health professionals and the community in primary, secondary and tertiary caries prevention

	Primary prevention	Secondary prevention	Tertiary prevention
Individuals	▶ Adequate oral hygiene ▶ Use of fluoride toothpaste ▶ Limit consumption of free sugars ▶ Regular preventive dental check-ups		▶ Regular use of preventively oriented oral health services
Oral health professionals	▶ Patient education ▶ Plaque control ▶ Diet counselling ▶ Topical application of fluoride ▶ Pit and fissure sealants	▶ Thorough examination detecting the early stages of caries ▶ Pit and fissure sealants ▶ Topical application of fluoride	▶ Prompt treatment of progressing lesions ▶ Minimum invasive treatment of lesions ▶ Continuing prevention for other sites
Community	▶ Oral health education programmes ▶ Community water fluoridation ▶ School fluoride tooth brushing or mouth rinse programme	▶ Periodic screening (ex: school screening) ▶ School sealant programme ▶ School fluoride varnish applications	▶ Provision of preventively oriented oral health services

Source (FDI World Dental Federation 2016).

1.7.2 Primary prevention and exposure to fluoride as a caries prevention measure

This thesis is focused on primary prevention of ECC. A recent WHO Expert Consultation on Public Health Intervention against Early Childhood Caries postulated that primary prevention should be the key to ECC management (WHO 2017b). Health promotion aimed at pregnant women, new mothers and primary caregivers should raise concerns at the common risk factors of ECC. WHO's recommendations on breastfeeding until six months of age, no added sugars for complementary feeding up to two years, and after that limited free sugars intake in accordance with the WHO guideline should be emphasized (WHO 2017b). Prevention of cariogenic feeding behaviours is one of the main

approaches to preventing ECC (Berkowitz 2003). Moreover, primary caregivers should be trained to provide proper toothbrushing with the right amount of fluoride toothpaste from the first primary tooth eruption, followed by early detection of early lesions of caries (WHO 2017b). A child should have a dental visit for comprehensive care in the first year of life, and any child at caries risk should have regular fluoride varnish applications (American Academy of Pediatric Dentistry 2019).

Exposure to fluoride is discussed in detail in this section, as the use of fluoride underpins the approaches used by the Childsmile programme in Scotland (see Section 1.11) and is also the basis of the Protecting Teeth @ 3 randomised controlled trial (see Section 1.11.6 for further information).

Fluoride in toothpaste is considered a main contributor to the decline in dental caries (Petersen and Ogawa 2016). However, there is a variety of other ways to deliver fluoride into the oral cavity. Fluoride can be delivered to the teeth systemically or topically (Carey 2014). Systemic fluoride from ingested sources can be deposited only in teeth that are forming. Topical fluoride influences the dynamic equilibrium between demineralisation and remineralisation of the tooth surface post-eruption. Fluoride can naturally occur in water or be added to water supplies. Other vehicles for fluoride include milk (Yeung et al. 2015), toothpastes (Walsh et al. 2019), drops, mouth rinses (Marinho et al. 2016), gels (Marinho et al. 2015), foams, and varnishes (Marinho et al. 2013, Carey 2014). The use of fluoride for the population based prevention of dental caries has been endorsed by WHO since the late 1960s (Petersen and Ogawa 2016).

Regular toothbrushing with fluoridated toothpaste is the principal non-professional intervention to prevent caries. The preventive effect varies according to different concentrations of fluoride in toothpaste, with higher concentrations associated with increased caries control (Walsh et al. 2019). Toothbrushing disrupts the dental biofilm and reduces bacterial numbers, while the fluoride in toothpaste helps to remineralize carious lesions (Seow 2018). Fluoride concentration in child toothpaste for anti-caries efficacy ranges from 1000 to 1500 parts per million (ppm) with a minimum of 800 ppm fluoride ion bioavailable (WHO 2017b). Brushing frequency should be at least twice per day.

The amount of fluoride toothpaste used in young children should be limited and an age appropriate amount should be used in order to promote safety (WHO 2017b).

Three systematic reviews that assessed the effectiveness of toothbrushing and fluoride varnish are highlighted below. Both of these interventions are delivered via the integrated Childsmile programme in Scotland (described in Section 1.11). A recent Cochrane systematic review (Walsh et al. 2019) assessed the effects of toothpastes of different fluoride strengths on preventing tooth decay in children, adolescents and adults. It was found that there was less new decay when toothbrushing with toothpaste containing 1000 to 1250 ppm or 1450 to 1500 ppm fluoride compared with non-fluoride toothpaste, and that toothbrushing with 1450 to 1500 ppm fluoride toothpaste reduced the amount of new decay more than 1000 to 1250 ppm toothpaste.

Topically applied fluoride varnish is a highly concentrated form of fluoride, which has been used as a clinician-applied caries preventive intervention in children and adolescents for many decades (Watt et al. 2018). An update of a Cochrane systematic review and meta-analysis of fluoride varnish (FV) application effectiveness (Marinho et al. 2013), which was based on a previous review (Marinho et al. 2002), indicated that the pooled prevented fraction estimate for deciduous teeth was 37% (95% CI 24%, 51%; P < 0.0001), based on 10 randomised controlled trial results. *"The prevented fraction is the proportion of disease occurrence in a population averted due to a protective risk factor or public health intervention"* (Gargiullo et al. 1995). The assessed body of evidence was of moderate quality. No significant association between estimates of the prevented fraction and the pre-specified factors of baseline such as caries severity, background exposure to fluorides, application features such as prior prophylaxis, concentration of fluoride, and frequency of application were found.

A recent systematic review that focused on the effectiveness of FV against caries specifically in preschoolers, found lower prevented fractions of 24% (95% CI 13%, 35%) or dmfs and 31% (95% CI 21%, 41%) for dmft data (de Sousa et al. 2019), in comparison with the 2013 Cochrane review (Marinho et al. 2013). The de Sousa and colleagues' review included 20 trials, and 10 of them were not included in

the 2013 Cochrane review. The results of 17 studies were included in meta-analyses. At the individual level, the pooled relative risk was found to be 0.88 (95% CI 0.81, 0.95), while the number needed to treat in a population of preschool children with 50% caries incidence was 17, which means that 17 children have to have a FV application in order to avoid new caries in one child. The authors found that the lower increment of caries in the varnish group was of one surface per child or less and commented that this difference was possibly clinically irrelevant. At the tooth level, no significant difference was observed between children who received FV and those who did not. The authors concluded that FV showed a modest and uncertain anti-caries effect in preschoolers and highlighted the need for more cost-effectiveness analyses carried out in different populations and application settings using updated FV effectiveness estimates.

1.7.3 Upstream, midstream and downstream prevention approaches

ECC prevention strategies can also be classified according to where they are placed with regards to the upstream/downstream continuum (Watt et al. 2004, Watt 2007, Watt 2012). Figure 1.8 illustrates upstream/midstream/downstream circumstances and risks for oral health inequalities.

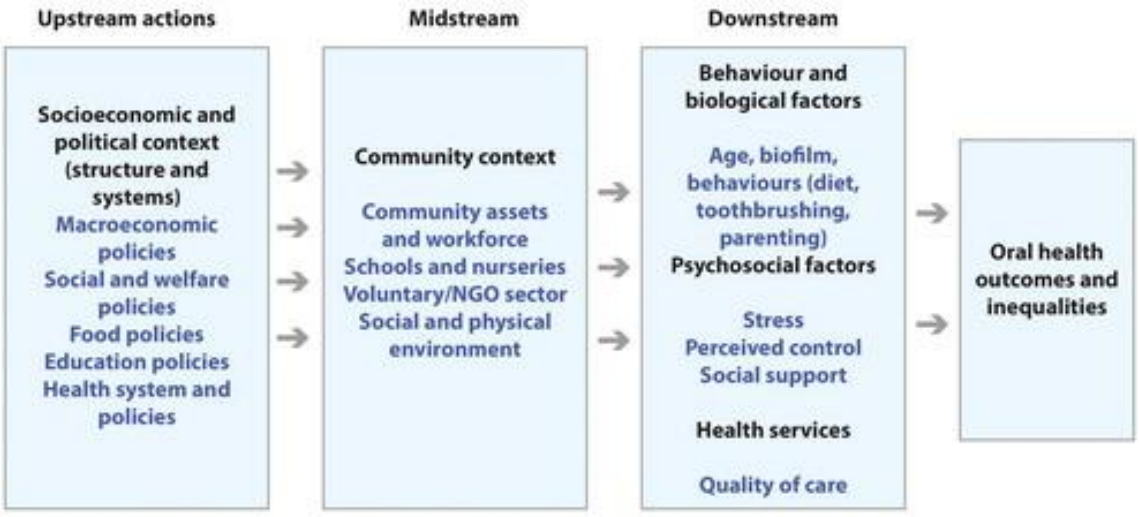

Figure 1.8 Model of circumstances and risks for oral health inequalities
Source (Watt and Sheiham 2012).

With regard to caries prevention, examples of upstream interventions are taxation of sugar-sweetened beverages and foods, sugar product reformulation, school food policies and implementing recommendations on marketing of foods and unhealthy drinks to children (Macpherson et al. 2019a), water fluoridation, milk and salt fluoridation (Pitts et al. 2017). The use of the common risk factors approach is recommended by the World Health Organization (WHO) (WHO 2017b), such as limiting free sugars intake and promoting breastfeeding, for controlling ECC together with child obesity. The WHO urges that population-wide strategies to reduce free sugars consumption are to be the key public health approach that should be a high and urgent priority (WHO 2017a). Besides, it recommends universally available and accessible population-wide prevention interventions, such as the use of fluoride and comprehensive patient-centred essential oral health care. At a population level, upstream approaches are likely to have a greater reach, greater effectiveness and higher cost-effectiveness than downstream interventions (Macpherson et al. 2019a), as upstream interventions impact broader social determinants of health (Watt 2007, Peres et al. 2019).

Examples of midstream approaches include community-run healthy food initiatives, integrating oral health into existing health services (for example, ante-natal classes, breastfeeding initiatives and child development checks), provision of free or subsidised toothbrushes and toothpastes through community clinics, as well as integrating health and wellbeing plans into the nursery and school curriculums (Macpherson et al. 2019a). Initiatives that can be delivered through nurseries and schools include healthy food policies, daily supervised toothbrushing and fluoride varnish programmes (Macpherson et al. 2019a).

Downstream interventions focus largely on individual behavioural factors (Watt and Sheiham 2012). Examples of such interventions include individual dietary and oral hygiene advice, fluoride varnish and fissure sealant applications or caries treatments delivered in dental practices, and one-to-one counselling based on motivational interviewing outside of dental practice settings (Public Health England 2014, Macpherson et al. 2019b).

Upstream interventions are universal in the sense that they benefit the whole population, whereas mid- and downstream interventions may be targeted at

higher risk groups. Examples of targeted approaches are fluoride varnish and fissure sealant applications in both nursery, school and dental practice settings, such as those included into the integrated Childsmile programme in Scotland (Childsmile 2020b) or the Designed to Smile programme in Wales (Designed to Smile 2020). Targeting higher risk groups may increase the cost-effectiveness of the intervention (Pitts et al. 2017).

This thesis focuses on primary prevention interventions, and in particular, the intervention that is described and evaluated in Chapters 5 and 6 (and briefly introduced in Section 1.11.6), which is a targeted fluoride varnish intervention, delivered through nursery settings, as a part of the integrated Childsmile programme in Scotland. Childsmile is described in more detail in Section 1.11.

1.8 Economics of early years interventions

A wide range of economic studies suggest that there are significant long term returns to early investment in children during the pre-birth period and up to the age of eight years old. However, these returns reduce the later the investment is initiated (Cunha and Heckman 2007, Heckman and Masterov 2007, Heckman 2008, Cunha and Heckman 2010, Scottish Government 2010a, Heckman 2011). Early investment in preventive programmes aimed at disadvantaged children is often more cost effective than later remediation which can be prohibitively costly (Doyle et al. 2007). Figure 1.9 plots the rate of return to human capital investment at different stages of the life cycle (Heckman 2008). It demonstrates that there is a higher rate of return at younger ages for a constant level of investment. By investing early, the benefits are enjoyed for longer, which in turn increases the return to investment (Doyle et al. 2007).

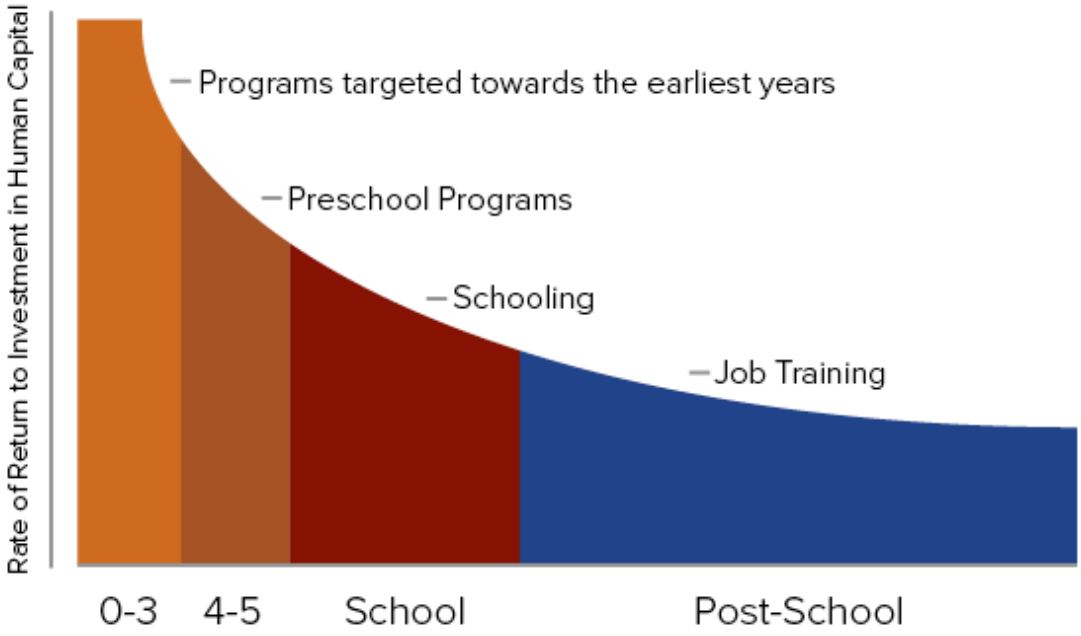

Figure 1.9 Returns to a unit dollar invested are highest in earliest years
Source (Heckman 2008).

Intervening early is important as several factors during early childhood, such as health, family structure and home environment can have an effect on the children's development, which will subsequently affect their human capital acquisition and later life outcomes (Doyle et al. 2007). The benefits of early years health interventions may extend beyond health, for example, improvements in literacy, job prospects and earnings (Masters et al. 2017).

The Financial Impact of Early Years Interventions in Scotland Report (Scottish Government 2010a) modelled the potential short term savings from investing in early years and early interventions from pre-birth to aged five and suggested that there were potential net savings of up to £37K per annum per child in the most severe cases and of approximately £5K per annum for a child with moderate difficulties in the first five years of life. The model also demonstrated that there are potential medium-term net savings to the public sector that can be realised 10 years after the early years period. It is estimated that the total potential saving resulting from 100% effective interventions early in life (pre-birth to aged eight) could initially be up to £131m per annum, in the medium term. In the longer term, a failure to effectively intervene to address the complex needs of an individual in early childhood can result in a nine-fold increase in direct public costs, when compared with an individual who accesses

only universal services (Scottish Government 2010a, Scottish Government 2010b).

1.9 Economics of early childhood caries

Early childhood caries (ECC) poses a significant economic burden to individuals, the health sector and society more broadly (Phantumvanit et al. 2018). The 2010 global direct financial costs associated with dental caries were estimated to be US$ 298 billion and indirect costs came to US$ 144 billion (WHO 2017a). Untreated caries was found to cause 12% of the global productivity losses due to dental diseases in 2015: $21.19 billion (11%) due to untreated caries in permanent teeth, and $0.90 billion (0.5%) to caries in deciduous teeth (Righolt et al. 2018).

Treatment of ECC often requires extensive restorative treatment, extraction of primary teeth, space maintenance (to prevent the unwanted movement of teeth that create malocclusions), and due to the young age of the child there can be substantial costs for sedation or general anaesthesia (Tinanoff et al. 2019).

Casamassimo and colleagues reviewed the literature for descriptions and quantification of morbidity associated with ECC and organized a wide range of studies into a visual model, which they called the ECC morbidity and mortality pyramid (Figure 1.10) (Casamassimo et al. 2009). The ECC morbidity and mortality pyramid has a low rate of associated fatality and a high rate of dysfunction, which causes the pyramid to have a broad base and narrow apex. The bottom, child and parent dysfunction, segment includes such elements as morbidity associated with treatment of ECC, days missed from school or work and inappropriate use of pain medicine. The middle segment, family associated morbidity, includes child's loss of school hours, parental loss of work time, costs associated with travelling to dental appointments, as well as eating and sleeping dysfunction and parental and family stress. The top segments include hospital costs (accident and emergency department costs, hospital admission and general anaesthesia costs), morbidity resulting from general anaesthesia, with death as a result of sedation or general anaesthesia, or from a developed infection, at the top of the pyramid.

Figure 1.10 Early childhood caries morbidity, costs and mortality pyramid
GA – General anaesthesia. Adapted from (Casamassimo et al. 2009).

Dental caries in young children has a significant impact on National Health Service (NHS) costs. In the 2013/14 financial year, the number of claimable courses of NHS dental treatment given to children in Scotland in general dental practices was around 520,000 (ISD Scotland 2014). Around a third (28%) of the claimable dental treatments provided to children were for prevention related to the Childsmile programme (such as toothbrushing instruction, dietary advice, and fluoride varnish applications), while 17% of the claimable treatments was treatment of deciduous teeth, including fillings and application of fissure sealant, around 15% were permanent fillings and 7% were tooth extractions (ISD Scotland 2014). In 2013/14, over £68 million was paid in child NHS general dental service fees in Scotland. The cost per head of child population was £66, while the cost per child registered at a dental practice was £72 (ISD Scotland 2014).

Treatment of early childhood caries under general anaesthesia (GA) in a hospital setting for extensive dental repair is especially costly (Phantumvanit et al.

2018). Treatment under GA may be for a variety of reasons, but the most common scenario is the need for multiple extractions and/or treatment for dental caries in a young child (Knapp et al. 2017). In the UK, dental caries remains the most common reason for a 5-9-year-old child to be admitted to hospital (Knapp et al. 2017, Godson et al. 2018). The dental GA procedure carries risks of morbidity and, very rarely, mortality to the child, and also places a considerable financial burden on the NHS (Knapp et al. 2017). In NHS England extraction of decayed primary teeth carried out under GA costs an estimated £28 million (Phantumvanit et al. 2018) to £36 million (Innes and Robertson 2018) annually. The estimated cost for providing extractions only under GA in children across three NHS Boards in Scotland, based on the number of referrals for treatment planning for extractions under GA in three centres in Dundee, Edinburgh and Glasgow in 2016, was approximately £1.7 million per year (SDNAP 2017).

With regards to the cost-effectiveness of oral health interventions in early childhood (0-5 years), the York Health Economics Consortium, UK, were commissioned to conduct a rapid evidence review (York Health Economics Consortium 2016e) and to develop a return on investment (ROI) tool (Public Health England 2016c) in partnership with Public Health England (PHE). Both the rapid review of evidence and the ROI tool were published in 2016. This rapid evidence review provided an update to the previous National Institute for Health and Care Excellence, UK (NICE) economic evidence review on oral health prevention measures (Public Health Advisory Committee 2014, Lord et al. 2015). The review specifically examined the cost-effectiveness of those oral health interventions with good evidence of effectiveness in reducing the average number of decayed, missing and filled teeth in 5-year-olds (Godson et al. 2018). The interventions included in the ROI tool were supervised tooth brushing, application of fluoride varnish, water fluoridation, provision of toothbrushes and paste and interventions provided in home visits by health workers. Using modelling data, the ROI tool was used to calculate the ROI of these five oral health improvement programmes at 5 and 10 years. The intervention with the highest ROI was water fluoridation, with £22 return at 10 years to each £1 invested, followed by targeted provision of toothbrushes and paste by post and by health visitors (over £7 return at 10 years). Targeted fluoride varnish

programme had one of the lowest returns with under £3 to each £1 invested (at 10 years) (Public Health England 2016b).

Of particular interest are studies that investigated the cost-effectiveness of fluoride varnish (FV) in young children, as FV applied in nursery settings is the intervention evaluated in the Protecting Teeth @ 3 trial, as described in Chapters 5 and 6 of this thesis. In recent years two relevant randomised controlled trials have been conducted in the UK. One was based in Northern Ireland and compared a combined fluoride intervention to the control group (prevention advice only) in general dental practice settings in children aged 2-3 years at baseline - Northern Ireland Caries Prevention in Practice (NIC-PIP) (Tickle et al. 2016, O'Neill et al. 2017). The other study, Seal or Varnish, was conducted in Wales on older children, aged 6-7 years, and compared fissure sealants (FS) and FV in preventing dental caries in first permanent molars (Chestnutt et al. 2017). In the Seal or Varnish trial, the interventions were delivered in mobile dental clinics in primary schools located in areas of high deprivation.

In the NIC-PIP trial, the combined fluoride intervention included FV, free toothbrush and fluoride toothpaste and standardized prevention advice. The intervention was provided at 6-monthly intervals over three years. The authors found no statistically significant difference between the study groups in the number of children converted from caries-free to caries-active state (the primary outcome), however, there was a statistically significant difference in dmfs in caries-active children in favour of the intervention. The authors concluded that the costs of providing a combined fluoride intervention outweighed savings in treatment over the three-year follow-up period. This intervention was unlikely to produce a cost-saving (O'Neill et al. 2017). Even with their evidence-based intervention and high levels of adherence, over a third of children developed caries.

In the Seal or Varnish trial FS was applied at baseline to first permanent molars, including part-erupted upper teeth. FS were checked at 6-monthly intervals and deficiencies were repaired. FV was applied to all eligible first permanent molars at baseline and at 6, 12, 18, 24 and 30 months (Chestnutt et al. 2017). The

results of the trial showed that over the three-year course of the study FV was less costly than fissure sealants, with similar outcomes achieved (the numerical differences in outcomes were not statistically significant). The total costs per child of the two technologies showed a small but statistically significant difference (£500 for FS, compared with £432 for FV, a difference of £68.13 in favour of FV, p = 0.033).

Both of the studies assessed cost-effectiveness of the interventions at three years follow-up and did not model costs and effects over a longer period of time.

1.10 General health- and oral health-related quality of life

Caries influences general health and quality of life across the entire life course (WHO 2019). Dental caries in children can lead to toothache or discomfort, compromise ability to eat and sleep and restrict socialising (White 2017, Nora et al. 2018, Phantumvanit et al. 2018, WHO 2019). Severe dental caries is associated with poor growth (WHO 2019).

Measuring participants' / patients' health-related quality of life (HRQoL) is essential for the conduct of economic evaluations. HRQoL is one of the main health outcome measures in economic evaluation of clinical trials (Petrou and Gray 2011, Hughes et al. 2016), as this is one of the outcomes of value to the patient / trial participant (Drummond 2001). Other practical applications of HRQoL measures include evaluating services for research, public health, and clinical purposes, and for describing and monitoring health status of populations (the results of which can be used to assess population needs, identify target populations, and priority setting) (Marshman and Robinson 2007). HRQoL measures together with clinical indicators, can jointly provide a more comprehensive assessment of the patient's general and/or oral health (Sischo and Broder 2011).

HRQoL is a complex, multidimensional concept, which includes social, emotional and physical functioning, related to the patient's health state. According to one of the definitions of HRQoL, it is "a combination of a person's physical, mental and social well-being; not merely the absence of disease" (NICE 2020b).

There are different types of HRQoL instruments (Drummond et al. 2005b, Drummond et al. 2015, Hettiarachchi et al. 2019). Generic HRQoL instruments can be applied to a wide range of different types of disease and different patient populations. These are comprehensive measures of HRQoL that are widely used and have established validity and reliability across different disease conditions and patient populations. Disease-specific HRQoL instruments are designed to assess HRQoL concerning specific diseases, medical conditions, or patient populations. Examples of disease-specific instrument are oral health-related quality of life (OHQoL) instruments. The generic and disease-specific QoL instruments that are developed based on classification system and preferences weights are known as preference-based instruments. These preference-based instruments are used in cost-utility analysis (Drummond et al. 2005b).

Methodological challenges to the measurement of HRQoL in children include problems caused by the changes that children undergo both physically and cognitively and the use of a proxy (parents, clinicians or teachers) (Marshman and Robinson 2007). Measuring HRQoL in young children under six years of age is specifically challenging (Bradlyn et al. 1996, Verstraete et al. 2020b). The consensus is that children under the age of five cannot provide reliable self-reports, and for them proxy reports should be used (Wallander et al. 2001, Varni et al. 2007, Matza et al. 2013).

OHQoL has important implications for the clinical practice of dentistry and dental research. It has wide-reaching applications in survey and clinical research. Assessment of OHQoL allows for a shift from traditional medical/dental criteria to assessment and care that focus on a person's social and emotional experience and physical functioning in defining appropriate treatment goals and outcomes (Sischo and Broder 2011).

Chapter 2, Section 2.5.2.4 contains more information on preference-based and non-preference-based HRQoL instruments, as well as on generic and disease-specific HRQoL instruments. Chapter 4 presents a review of general HRQoL and OHQoL instruments used in preschool children, aged 3-5 years, while the introduction section to Chapter 4 provides definitions and further details on general HRQoL (Section 4.1.1) and OHQoL (Section 4.1.2).

1.11 Childsmile

Childsmile is the national child oral health improvement programme for Scotland. It was developed as pilot studies from 2006, building on an established national supervised toothbrushing programme in nursery schools. By 2011, an integrated programme was in place in all NHS Boards across the country.

Responsibility for the National Health Services (NHS) in Scotland is a devolved matter and therefore rests with the Scottish Government. The Scottish Government decides what resources are to be devoted to the NHS, in the context of devolved public expenditure. It also sets national objectives and priorities for the NHS, signs delivery plans with each NHS Board, monitors performance, and supports NHS Boards to ensure achievement of these objectives (NHS Scotland 2020). There are 14 territorial NHS Boards in Scotland. Each of them is responsible for the protection and the improvement of their population's health and for the delivery of frontline healthcare services.

The funding for the delivery of a range of preventive services within the territorial NHS Boards, including the Childsmile programme, is delivered through a single source called the Outcomes Framework (Scottish Government 2017). The Framework provides greater local flexibility on decisions on how to maximise the value from this resource against clearly defined outcomes. The Framework has a strong focus on delivering strategic priorities such as prevention and reducing health inequalities. The Outcomes Framework is allocated to NHS Boards at the start of each financial year with a summary of clearly defined outcomes. NHS Boards have the flexibility to meet agreed outcomes within the overall framework value, as it is not prescriptive how the money should be allocated locally to each service. Economic evaluations of preventive programmes/interventions can help the decision makers to allocate these limited resources effectively so that a greater benefit is achieved.

Childsmile aims to improve the oral health of children in Scotland and reduce inequalities both in dental health and access to dental services. Since 2011, Childsmile has been delivered as an integrated programme in all (n = 14) Health Board areas throughout Scotland. The programme has developed and delivers

oral health improvement interventions both within and outside traditional dental clinical settings – in education establishments, community settings, other healthcare settings (integration to Health Visitor Early Years Pathway), and children's homes (Macpherson et al. 2019b). The main features of the Childsmile programme, and its position within the upstream/downstream continuum are shown in Table 1.4.

Childsmile is funded by the Scottish Government and has four main elements (Childsmile 2020b):

- Supervised toothbrushing programme;
- Fluoride varnish in nursery and school programme;
- Community interventions (involving Health Visitors and Dental Health Support Workers);
- Dental primary care (in dental practices).

These are described in detail below, adapted from (Macpherson et al. 2019b).

Table 1.4 Main Childsmile interventions within the upstream/downstream continuum

Upstream
Influencing Public Health Policy at national level: • Contribute to development of healthy food & drink regulations in education settings • Change to national primary dental care contract for children (prevention-orientated)
Midstream
Oral Health Training for wider workforce: • Training to national standards for nursery and school staff • Guidance for Health Visitors
Supervised toothbrushing in nursery and school settings • National standards: universal in nurseries; targeted in schools
Universal and targeted provision of toothbrushes/paste • National contract: distribution via education, health and other community settings
Targeted community-based fluoride varnish programmes • National standards: nursery and school settings
Mid/Downstream
Integration of oral health into targeted home visits by health workers • Health visitors & DHSWs strengthening core skills, coping strategies
Signposting/linking and engagement with community initiatives • eg community engagement, food co-operatives, infant feeding programmes

Source (Macpherson et al. 2019b).

1.11.1 Supervised toothbrushing programme

Every three- and four-year-old child attending nursery (whether it is a local authority, voluntary or private nursery) is offered free, supervised toothbrushing. National toothbrushing standards have been developed and are closely followed, on a daily basis, by nursery staff (Childsmile 2019b, Childsmile 2020a). Oral health personnel from the Public Dental Service are available to provide training and support. The products (toothbrush and 1450ppm fluoride toothpaste) are provided by a nationally procured contract to ensure consistency and cost-savings across Scotland.

Supervised toothbrushing continues into the first two years (5–6-year-olds) for targeted primary schools, namely, those situated in areas with the highest level of deprivation in each NHS Health Board.

To promote home toothbrushing, every child is also provided with a dental pack (containing a toothbrush and a tube of 1450 ppm fluoride toothpaste) on at least six occasions by the age of five, initially by the health visitor and then via nursery. Children also receive a free-flow feeder cup by one year of age (Macpherson et al. 2019b).

Childsmile's supervised nursery toothbrushing programme has been shown to be both clinically effective and cost-effective (Macpherson et al. 2013, Anopa et al. 2015).

1.11.2 Fluoride varnish in nursery and school programme

This segment of the Childsmile programme delivers, via nursery and primary school settings, the application of fluoride varnish to the teeth of children aged three to at least eight years who are identified as living in the most deprived areas. It covers a minimum of 20% of children from each NHS Health Board. Educational establishments are targeted in order of those with the highest proportion of children living in the most deprived local quintile as defined by the Scottish Index of Multiple Deprivation (SIMD) (Scottish Government 2016b). Twice-yearly fluoride varnish applications are provided by Childsmile dental nurses. These extended duty dental nurses have been trained by NHS Education

for Scotland in fluoride varnish application technique. As part of the process, children who require further assessment and possible dental care are identified and their parents receive a letter informing them of their child's dental need (Macpherson et al. 2019b).

In Scotland uptake of funded Early Learning and Childcare (ELC) / nursery places for eligible three- and four-year-olds is very high. As of September 2019, an estimated 98% were registered at ELC (Scottish Government 2019c). The initial aim of the nursery FV component of Childsmile was to reach 20% of the nursery age population (three and four year olds) by targeting nurseries with the highest proportion of children living in the most deprived areas within each NHS Board (Macpherson et al. 2019a). However, many NHS Boards went over and above that 20% target. In the 2018/19 academic year, 38% of the total number of nurseries participated in FV across Scotland, while 44% of the three- and four-year-old population were targeted to receive FV in nursery settings. 31% of three- and four-year-olds received at least one FVA, while 18% received two or more FVAs within 2018/19 (Childsmile Central Evaluation & Research Team 2019). In the same year, 47% of the three- and four-year-olds population in SIMD1 (the most deprived quintile) received at least one FVA across Scotland, while 26% received two or more FVAs within that year (Childsmile Central Evaluation & Research Team 2019). The proportion of SIMD1 children receiving FVAs was the highest out of all SIMD quintiles with the proportions gradually decreasing along the SIMD quintiles (to the lowest proportion for SIMD5 children, the least deprived quintile: 17% received at least one FVA, and 10% of them received two or more FVAs).

Previous research has highlighted the difficulties in identifying and reaching all of those individuals most in need of an intervention, particularly when applied in a nursery/school (or other group) setting (Brewster et al. 2013). Firstly, efforts must be made to prevent stigmatising individual children, therefore Childsmile ensures that all children within a targeted nursery are offered the intervention irrespective of whether they are considered at increased-risk or not. Secondly, all public health interventions must operate within the constraints of limited financial resources and therefore a realistic cut-off for the group to receive the intervention must be chosen (20% of the population in the case of the Childsmile

FV programme). Taking into account the abovementioned constraints, a previous study found that, at a Scotland level, only around 50% of those targeted by the FV intervention delivered in primary schools were considered at increased-risk of caries, irrespective of the method used or definition of increased-risk. This means that almost 50% of those targeted to receive the intervention were not considered at increased-risk (Brewster et al. 2013).

1.11.3 Community interventions involving Health Visitors and Dental Health Support Workers

Every new-born child in Scotland is linked to Childsmile via the universal child health surveillance system within the Universal Health Visitor Early Years Pathway (Scottish Government 2015). Health Visitors see all children and their parents/carers on a regular basis between birth and five years. Health Visitors provide advice on oral health, distribute a dental pack, and encourage dental attendance from a young age. Where they feel additional support may be required to promote oral health, they make a referral to a community-based dental health support worker (DHSW) (Macpherson et al. 2019b).

DHSWs are embedded within the more disadvantaged communities and offer peer support to families with young children in the family home. They work closely with health visitors, dental practices, and the Public Dental Service (who co-ordinate and administer the Nursery and School components of the programme). They are aware of, and engage with, agencies in their local communities which can help to support family life and parenting skills, e.g. access to healthy foods, promoting coping skills/self-esteem, and thus facilitate and enable the implementation of positive child oral health promoting behaviours. The DHSWs can also provide support to these groups and assist them to incorporate oral health into their activities and, additionally, can undertake social prescribing to link families into these organizations, as deemed appropriate at an individual level (Macpherson et al. 2019b).

DHSWs provide the following: a) Tailored support and advice to promote and enable oral health in the family home; b) Linking to dental services and facilitating child attendance at a dental practice; and c) Engaging with and signposting/linking to other community organizations and initiatives via social

prescribing (e.g. food co-operatives, infant feeding programmes, parenting skills classes, debt management advice agencies) (Macpherson et al. 2019b).

1.11.4 Dental primary care

In 2011, payments were introduced into the NHS primary dental care contract in Scotland for preventive items of care, including fluoride varnish, and advice to support and enable plaque control via toothbrushing with a fluoride-containing toothpaste and promoting healthy eating in the family home (Childsmile 2011). This programme of preventive care should be tailored to meet the needs of the individual child and be delivered by any appropriately trained dental team member. The clinical care includes twice-yearly fluoride varnish applications from two years of age and, as children age, there are opportunities for fissure sealant applications on first permanent molar teeth.

A major aim of the programme is to replace very brief, standardized 'health education' messages with meaningful, tailored support for families. Identification of social needs which can best be met by other community groups and organizations should be identified and linking to such organizations and groups promoted, as appropriate (Macpherson et al. 2019b).

1.11.5 Economics of the nursery toothbrushing component of Childsmile

A cost analysis of the nursery toothbrushing component of Childsmile has previously been conducted (Anopa et al. 2015) covering a 9-year period from 2001 to 2009. It was estimated that the cost of the nursery toothbrushing programme in Scotland was £1.8m per year (Figure 1.11). The estimated cost of dental treatments in 2001, the baseline year, was £8.8m, while in 2009 it decreased to £4m. The estimated annual savings ranged from £1.2m in 2003 (14% of costs in 2001/02) to £4.7m in 2009 (54%). In the eighth year of the toothbrushing programme the expected savings were more than two and a half times the costs of the programme implementation.

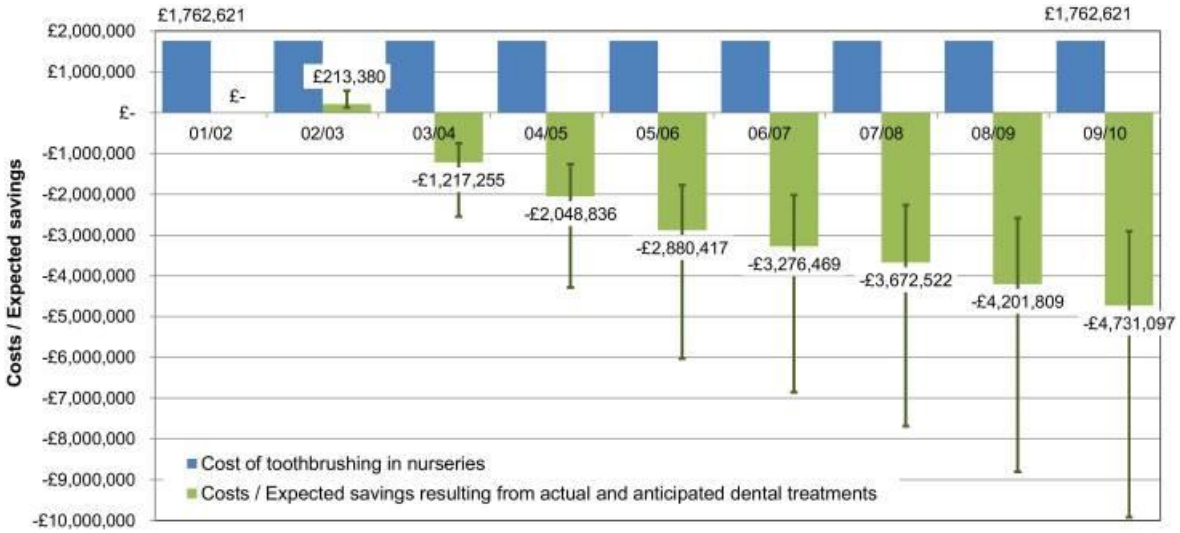

Figure 1.11 Annual cost of nursery toothbrushing programme in Scotland and costs / expected savings resulting from actual and anticipated dental treatments – in comparison with 2001/02 dental treatment costs

Note: The whiskers represent costs / expected savings resulting from actual and anticipated dental treatments in the case of a “low general anaesthesia cost” and “high general anaesthesia cost” sensitivity scenarios.

Source (Anopa et al. 2015).

Population standardised analysis by deprivation groups showed that the largest decrease in modelled costs was for the most deprived cohort of children. The results of the population standardised analysis per hypothetical cohort of 1000 children per deprivation group (Depcat) are shown in Figure 1.12. For the most deprived (Depcat 7) the savings resulting from the decrease in the total cost of treatment in primary teeth from 1999 to 2009 was £137K (50% of the 1999 costs for the most deprived), whereas for the least deprived cohort (Depcat 1) the expected saving was £30K (55%) – see the Total Cost, yellow bars, graph in Figure 1.12.

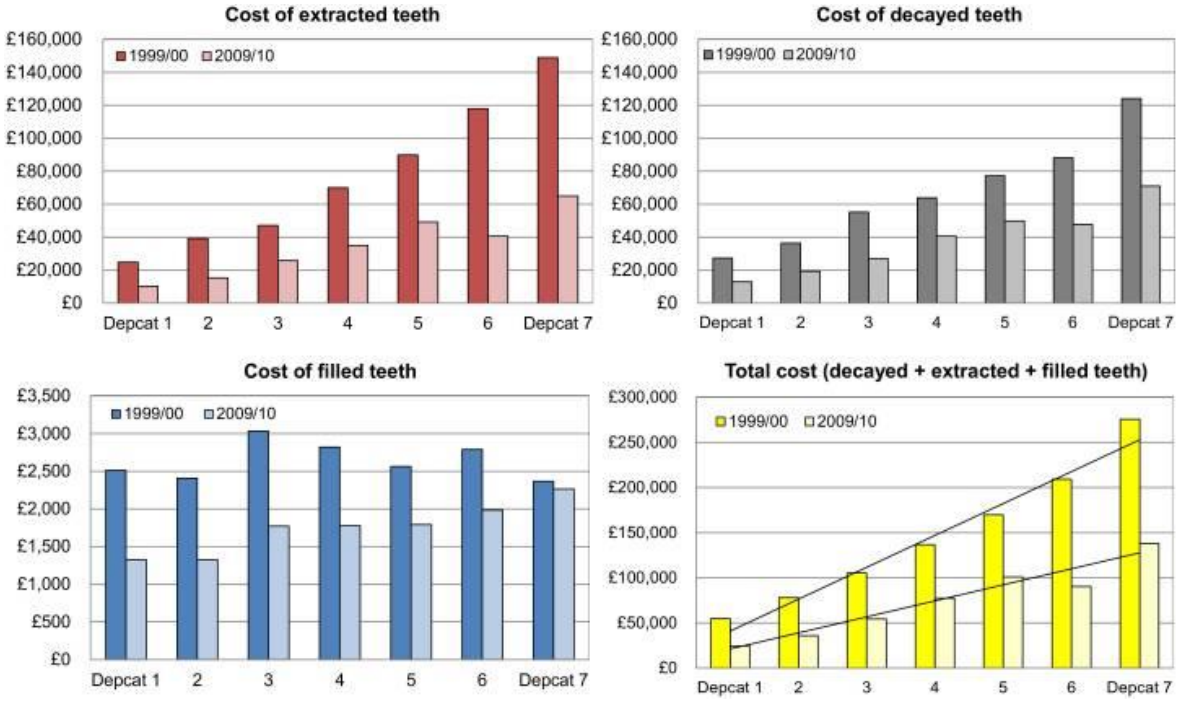

Figure 1.12 Costs of decayed, extracted and filled teeth per 1000 population, by Depcat (Depcat 1 = least deprived, Depcat 7 = most deprived).

Source (Anopa et al. 2015).

The other components of Childsmile have not been previously assessed economically. One of the aims of this thesis was to conduct an economic evaluation alongside a randomised controlled trial of the nursery fluoride varnish component of Childsmile – the Protecting Teeth @ 3 randomised controlled trial, which is described in brief in the section below.

1.11.6 Protecting Teeth @ 3 randomised controlled trial

Previous research has shown that the universal nursery toothbrushing programme in Scotland is both effective (Macpherson et al. 2013) and cost-saving (Anopa et al. 2015). However, it is unknown whether there are any *added* benefits of fluoride varnish applied in nursery settings over and above the effects of the nursery toothbrushing and other components of Childsmile (as described in Section 1.11), and whether the application of fluoride varnish in nurseries is cost-effective. The Protecting Teeth @ 3 randomised controlled trial (PT@3) was designed to answer these two questions. Further details on the PT@3 Study description and methods, including the economic evaluation methods, can be found in Chapter 5. While Chapter 6 contains the results of the economic evaluation of the PT@3 Study.

1.12 Economic evaluation in child caries prevention – the status quo

Limited research has been conducted in the field of economic evaluation (EE) in dentistry, including paediatric caries prevention (Marino et al. 2013). Although the numbers of published EEs in dentistry have increased in the last two decades, the quality of such studies is, however, variable (Kallestal et al. 2003, Marino et al. 2013, Tonmukayakul et al. 2015). A number of methodological limitations have been identified, such as incorrect use of labels for types of economic evaluation, inadequate sensitivity analyses, limited information provided on adjustments for discounting, lack of information on the perspective of the analysis, and insufficient details of outcomes and costs measurement and valuation (Marino et al. 2013, Tonmukayakul et al. 2015, Faggion and Tonmukayakul 2016, Rogers et al. 2019). A systematic review of the application of decision analytical modelling in the context of dental caries, which also assessed the methodological quality of the included publications, concluded that the methodological quality of the published studies was unsatisfactory and recommended that future modelling studies should adhere to good practice guidelines (with respect to data quality evaluation, utility values incorporation, and uncertainty analysis in decision analytical modelling studies) (Qu et al. 2019). A recent systematic review of EEs in child oral health research, which included full EE studies involving children aged 18 years old and under (Rogers et al. 2019), highlighted that a wide range of outcome measures was employed across the reviewed studies, which prevented inter-study comparisons. Lack of meaningful involvement of children and of consideration of their own perspectives and preferences were also emphasised.

Several systematic and non-systematic reviews have indicated that the quality of reporting as well as study design in the field of economic evaluation in the child oral health area and in dentistry overall needs to be improved (Kallestal et al. 2003, Marino et al. 2013, Christell et al. 2014, Mejare et al. 2015, Tonmukayakul et al. 2015, Faggion and Tonmukayakul 2016, Ladewig et al. 2018, Qu et al. 2019).

Experiences and health-related behaviour patterns in early life are known to affect oral health throughout the life-course. Consequently, calls have been made for priority to be given to interventions targeting early ages (ICOHIRP 2015). However, recent reviews of EEs of oral health improvement programmes and interventions (Coffin et al. 2013) and of cost-utility analyses of oral health interventions (Hettiarachchi et al. 2018) identified only a handful of studies conducted in preschool populations. Literature searches revealed only one non-systematic review that looked at the evidence on the cost-effectiveness of interventions to improve the oral health of younger children, aged 0-5 years (York Health Economics Consortium 2016e). This review found only five studies, which met the inclusion criteria.

1.13 Thesis aims, objectives and research questions

This thesis aims to add to the existing body of knowledge in the field of economics of primary caries prevention in children aged 2-5 years. As indicated earlier in this chapter, there is a lack of high-quality EEs alongside clinical trials that have used rigorous methodology and adhered to good practice guidelines. In order to address this gap in the existing literature, this PhD project was initiated.

1.13.1 Overarching aims and research questions

The overarching aim of this thesis is to explore the role of economic evaluation in primary caries prevention in preschool children aged 2-5 years. This aim will be met through answering the following research questions.

The first question is a generic one, which aims to review the knowledge base:

1) What is the existing evidence in the field of economic evaluation of primary caries prevention in children aged 2-5 years?

Research questions 2 and 3 are specifically related to the economic evaluation of the PT@3 trial:

2) Which general health and oral health-related quality of life measures (both parental proxy and child self-report) have been used in 3-5-year-old populations? And which of these measures are best suited to be used in the Protecting Teeth @ 3 randomised controlled trial?

3) Is the application of fluoride varnish delivered in nursery settings in addition to the other usual Childsmile components (treatment as usual) cost-effective in comparison with treatment as usual only?

Consequently, this thesis constitutes three empirical work segments:

1) A systematic review of economic evaluations of primary caries prevention in 2-5-year-old preschool children (presented in Chapter 3).

2) A non-systematic review of instruments for measuring general and oral health-related quality of life in 3-5-year-old children (Chapter 4).

3) Economic evaluation of the Protecting Teeth @ 3 randomised controlled trial (Chapters 5 and 6).

The specific objectives for each of the empirical chapters are further described below.

1.13.2 Chapter Three aims and objectives

The overall aim of Chapter 3 is to conduct a systematic review of scientific papers on economic evaluations of primary caries prevention in preschool children aged two to five years and to further evaluate the reporting quality of the included full EE studies.

The specific objectives of Chapter 3 are as follows: a) To describe and summarise currently available scientific literature on economic evaluations of primary caries prevention in preschool children aged two to five years; b) To evaluate the reporting quality of the included full economic evaluation studies, using a quality assessment tool developed for appraisal of economic evaluations.

1.13.3 Chapter Four aims and objectives

The main research questions for the general health and oral health-related quality of life (GHQoL and OHQoL, respectively) instruments review are:

> What are the existing GHQoL and OHQoL instruments for the age group three to five years? And which of these are best suited to be used in the Protecting Teeth @ 3 randomised controlled trial, which investigates the effectiveness and cost-effectiveness of fluoride varnish application in nursery settings?

The specific objectives of this quality of life instruments review are as follows:

a) To identify, assess and provide descriptive characteristics of the existing GHQoL instruments that have been developed for three- to five-year old children, except for the GHQoL instruments that were developed specifically for children with chronic conditions. Both proxy- and child self-report measures are to be included.

b) To identify, assess and provide descriptive characteristics of the existing OHQoL instruments that that have been developed for three- to five-year old children. Both proxy- and child self-report measures are to be included.

c) To produce descriptive tables comparing the identified GHQoL and OHQoL instruments.

d) On the basis of the above, to provide recommendations on which GHQoL and OHQoL instruments would be best used in the Protecting Teeth @ 3 trial for inclusion in the economic evaluation.

1.13.4 Economic evaluation of Protecting Teeth @ 3 trial – Aims and objectives (Chapters 5 and 6)

The economic evaluation aim was to assess the cost-effectiveness of preventive fluoride varnish in the context of the Childsmile programme. Namely, to

estimate the cost-effectiveness of the fluoride varnish (plus treatment as usual) intervention compared with treatment as usual only (control) in three ways:

a) To conduct a cost–utility analysis (CUA) comparing the incremental costs and utilities of the fluoride varnish (plus treatment as usual) intervention with treatment as usual only over a 24-month period.

b) To conduct a cost-effectiveness analysis (CEA) comparing the incremental costs and effects (oral health improvement or worsening, as measured by the d3mft index) of the fluoride varnish (plus treatment as usual) intervention with treatment as usual only.

c) To conduct a cost-consequence analysis (CCA) including available costs and outcome measures from the results of the CUA and CEA, as well as other general health and oral health-related quality of life measures employed.

1.14 Thesis structure

Following this introduction chapter, Chapter 2 provides a general overview of economic evaluation (EE) approaches and methods. It introduces general economics concepts and EE, covers EE frameworks, costs and costing approaches, outcome measures and valuation of outcomes. It also outlines technical issues in EE, reporting and presentation of EE results, various vehicles for EE, and, finally, covers the specifics of EE of public health interventions.

Chapter 3 is a systematic review of economic evaluations of primary caries prevention in 2-5-year-old preschool children. It addresses the first research question of this thesis.

Chapter 4 addresses the second research question by presenting a non-systematic review of instruments for measuring general and oral health-related quality of life in 3-5-year-old children. The results of this review helped to identify the instruments to be used in the Protecting Teeth @ 3 randomised controlled trial.

Chapter 5 provides a rationale for and describes the methods of the economic evaluation of the Protecting Teeth @ 3 randomised controlled trial, while Chapter 6 contains the results of this EE as well as a discussion of the results.

Chapter 7 contains an overall discussion, recommendations and conclusions.

Chapter 2 Economic evaluation approaches and methods

2.1 Introduction to Chapter 2

The population of the United Kingdom (UK) has increased over recent decades as well as aged. In 2017, the number of people aged 85 years and over was more than three times greater than it was in 1971 (Public Health England 2018b). People are living longer, but the increase in healthy life expectancy (years spent in good health) has not kept pace with life expectancy. As a result, people are spending more years in poor health (Public Health England 2018b). According to the data from the Office for National Statistics, estimated healthcare spending per person in the UK, in real terms, almost doubled between 1997 and 2018, rising from £1,672 per person in 1997 to £3,227 in 2018, as healthcare expenditure growth greatly exceeded population growth (Office for National Statistics 2020). The Organisation for Economic Co-operation and Development (OECD) report pressures on health expenditure are increased by new health technologies, which extend the scope, range and quality of medical services; rising incomes, which cause higher expectations on the quality and choice of care; and population ageing (OECD 2015). This continually rising trend in spending is viewed to be fiscally and economically unsustainable (Appleby 2013, OECD 2015).

OECD argue that healthcare is one of the most complex expenditure areas and is considered to be the hardest area in which to contain costs. Moreover, there are many stakeholders who intervene between the patient and the public resources that finance the healthcare, such as purchasers, a wide range of service providers, providers of medicines, tests and equipment and other intermediaries (OECD 2015). In the UK, financial pressures on the National Health Service (NHS) are severe and show no sign of easing (Lafond et al. 2016, Robertson et al. 2017). This was the case even before the COVID-19 pandemic, with the pandemic multiplying these pressures further (Griffin 2020, Mahase 2020). There is a growing gap between demand for services and resources available. UK evidence shows that while some acute services were relatively protected in their

funding, some community-based and public health services have been cut (Robertson et al. 2017).

In view of the above, NHS commissioners, local authorities and local public health teams are under budget pressures and facing increasingly challenging decisions over what services to invest in and disinvest from. Health economic methods and economic evaluation of healthcare programmes can aid decision-makers with their difficult choices in allocating scarce healthcare resources, setting priorities and shaping health policy. Economics is about allocating scarce resources, and the three elements fundamental to understanding the economic perspective are choices, scarce resources and alternative uses of these scarce resources (Miller 2009). Health economics uses economic principles to understand the production of health and health services and to inform decisions about scarce resources allocation in healthcare through the use of economic evaluation (Public Health England 2018a). Given the failure of the market system in healthcare to allocate resources optimally, there is a need for economic evaluations to 'reconstruct' the missing market and to facilitate decision- and policy-making in this area (Weatherly et al. 2009, McIntosh et al. 2010).

Research indicates that investing in prevention strategies may bring substantial economic benefits. Research shows that many public health interventions (PHIs) are good value for money (Owen et al. 2012, Masters et al. 2017). Yet, prevention needs a stronger economic case (in comparison with an economic case for treatment) supported by a larger number of high-quality economic evaluations of individual prevention programmes and interventions. With regards to caries prevention interventions in children, previous reviews have indicated that the quality of reporting as well as study design of economic evaluations in the area needs to be improved (Kallestal et al. 2003, Marino et al. 2013, Hettiarachchi et al. 2018, Rogers et al. 2019).

As it was previously described in Chapter 1, early childhood caries (ECC) poses a significant economic burden to health services (Phantumvanit et al. 2018), as it often requires extensive restorative treatment and/or tooth extractions, and there can be substantial costs for sedation or general anaesthesia (Tinanoff et al. 2019). In the UK, dental caries is the most common reason for a 5-9-year-old

child to be admitted to hospital (Knapp et al. 2017, Godson et al. 2018). ECC has a significant impact on NHS costs (ISD Scotland 2014, Innes and Robertson 2018, Phantumvanit et al. 2018). However, childhood caries prevention programmes can be highly cost-effective and even cost-saving. For example, the nursery toothbrushing component of Childsmile has been shown to be not only cost-saving but inequalities narrowing, with the largest decrease in costs happening in the most deprived cohort of children (Anopa et al. 2015).

This chapter presents general economics and health economics concepts and introduces terms and methodological approaches used throughout this thesis. Section 2.2 starts with the introduction of economics and basic economics concepts, while Section 2.3 introduces the concept of market failure and explains how economic evaluation helps to reconstruct the missing market in healthcare. This is followed by Section 2.4, which describes what economic evaluation (EE) is. EE frameworks are covered in Section 2.5, namely, cost-effectiveness analysis (CEA), cost-utility analysis (CUA), cost-benefit analysis (CBA), cost-consequence analysis (CCA) and cost-minimisation analysis (CMA). CUA and the related concepts of quality-adjusted life years and health-related quality of life are covered in more detail compared with the other types of EE, as CUA is the approach primarily used in the EE of the Protecting Teeth @ 3 trial, as a part of this thesis (Chapters 5 and 6).

EE perspectives, costing approaches and cost types are covered in Section 2.6; followed by technical issues in EE (Section 2.7) such as time horizon, discounting, uncertainty and missing data; existing guidelines for reporting and presentation of EE results (2.8); and vehicles for economic evaluation: EEs alongside clinical trials, decision tree models and Markov models (2.9). Section 2.10 presents EEs of PHIs, including specific challenges, NICE's health economics public health guidance and an overview of cost-effectiveness of PHIs.

2.2 Economics and economic concepts

This section will introduce some basic economics concepts, such as a definition of economics, the concepts of scarcity, opportunity cost, priority setting, allocative and technical efficiency, equity, the margin and incremental analysis.

2.2.1 What is economics?

According to one of the definitions (by the Nobel Prize winning economist, Paul Samuelson), economics is *"the study of how men and society end up choosing to employ scarce resources that could have alternative uses"* (Samuelson, 1980).

The definition below, also by Paul Samuelson, adds detail:

> *"The study of how men and society end up choosing, with or without the use of money, to employ scarce productive resources that could have alternative uses, to produce various commodities and distribute them for consumption, now or in the future, among various people and groups in society. It analyses the costs and benefits of improving patterns of resource allocation"* (Samuelson 1948).

Put simply, economics is about allocating scarce resources (Miller 2009). Scarcity, choice and opportunity cost (alternative uses of resources) are the three elements fundamental to understanding the economic perspective (Miller 2009, Listl et al. 2019). Economics is viewed as "the science of choice", and it can help to guide healthcare decision-makers in using resources in the best manner possible (Mitton and Donaldson 2009).

In her book Health Economics: An Introduction to Economic Evaluation, Gisella Kobelt defined health economics as *"the application of the theories, tools and concepts of the discipline of economics to the topics of health and health care. …health economics is concerned with the allocation of scarce resources to improve health."* p.1 (Kobelt 2013).

In the sections below several major economic concepts are covered: scarcity, priority setting, opportunity cost, economic efficiency (allocative and technical efficiency), margin, incremental analysis and market failure.

2.2.2 Scarcity

Scarcity is known as the economic problem and is the cornerstone of economics as a discipline (Raiklin and Uyar 1996, Miller 2009). Existing resources (such as

staff, time, facilities, equipment and knowledge) are scarce and choices must be made concerning their deployment, as it is impossible to produce *all* desired outputs at the same time (Drummond et al. 2015). Scarcity exists because *"needs, wants, demands or desires will always be greater than resources available to meet them"* p.6 (Miller 2009) and *"because it is human nature for people to want more than they have"* p.3 (Ruffin and Gregory 1993).

In the presence of scarcity choices must be made about how to use the available resources (Listl et al. 2019). Economic evaluation (EE) provides a means of organized consideration of the factors involved in a decision to commit resources to one use instead of another (Drummond et al. 2015). It attempts to reconstruct the "missing market" where market failure has occurred. Market failure and the purpose of EE are discussed in more detail in Section 2.3.

2.2.3 Opportunity cost

One of the fundamental concepts of health economics is opportunity cost. Scarcity of resources means that using resources on one health care activity involves sacrificing activity somewhere else. *"The opportunity cost of undertaking an activity is defined as the benefits that must be foregone by not allocating resources to the next best activity"* p. 198 (Goodacre and McCabe 2002). If the benefits generated from the way resources were chosen to be used exceed the benefits generated by using the same resources in their most productive alternative uses (namely, the opportunity cost), then the available resources have been used efficiently (Listl et al. 2019). Within healthcare there is a strong recognition of the need to consider scarcity of resources and opportunity cost. Every choice, action, or decision about the use of resources has an associated forgone opportunity – the value of those resources in their next best use (Edwards and McIntosh 2019).

2.2.4 Priority setting

Priority setting, or rationing is an unavoidable consequence of scarcity (Shiell et al. 2002). As there are insufficient resources to meet all needs, some needs must be left unmet and priority should be given to services that best meet one's objectives. Priority setting refers to the process of deciding which needs should

be met and which needs cannot be met (at least not immediately) (Shiell et al. 2002).

According to Donaldson and Mooney (1991), *"the aim of priority setting is to ensure that the health benefits resulting from health care are maximised and that the opportunity costs of health care are minimised"* p.1529 (Donaldson and Mooney 1991). Priority setting is done by comparing health care interventions with each other in terms of both health gains produced and resources spent. The economic approach to priority setting addresses two efficiency questions: 1) Is a health care intervention worthwhile? (allocative efficiency) 2) Given that it is worthwhile, what is the best way of providing it? (technical efficiency) (Donaldson and Mooney 1991).

There are several approaches to priority setting, such as economic evaluation, health technology assessment, programme budgeting and marginal analysis, quality adjusted life year (QALY) and league tables (Mitton et al. 2003). The current chapter is concerned specifically with economic evaluation approaches.

At a country level, priority setting approaches can be divided into those centred on outlining principles that guide prioritisation (for example, in Norway, the Netherlands, Sweden, and Denmark) versus those that established bodies that would actually recommend what services should be provided within the system define practices (such as the UK, Israel and New Zealand) (Sabik and Lie 2008).

In the UK, the National Institute for Health and Care Excellence (NICE) is an independent organisation that provides evidence-based national guidance and advice to improve health and social care (NICE 2020a). NICE's role is to improve outcomes for people who use the National Health Service (NHS) and other public health and social care services. NICE work across three areas: 1) It produces evidence-based guidance and advice for health, public health and social care practitioners; 2) It develops quality standards and performance metrics for those providing and commissioning health, public health and social care services; and 3) It provides a range of information services for commissioners, practitioners and managers across health and social care (NICE 2020a).

2.2.5 Allocative efficiency, technical efficiency and equity

Each "health" economy faces three main economics questions (Edwards and McIntosh 2019):

The first one is based on the concept of "allocative efficiency", which aims to maximise social welfare in relation to defined social goals, through choices about how scarce resources may best be used: "*What (health) goods, services, and environments should society produce?*" (Edwards and McIntosh 2019).

With allocative efficiency, all objectives compete with each other for implementation. Allocative efficiency entails deciding what objectives have to be met and the extent to which they have to be met, rather than *how* to achieve these objectives (Shiell et al. 2002). Allocative efficiency requires making a value judgement about the relative merits of different objectives (Goodacre and McCabe 2002). Allocative efficiency in health care is achieved when it is not possible to increase the overall benefits produced by the health system by reallocating resources between programmes (Shiell et al. 2002).

The second question is based on "technical efficiency", which explains the relationship between inputs and outputs in the production process. "*What technical means of production should be used to produce these (health) goods, services, and environments?*" (Edwards and McIntosh 2019). Technical efficiency entails achieving a given objective with the least possible expenditure (Goodacre and McCabe 2002). Technical efficiency is linked to cost-effectiveness: the combination of technically efficient inputs that minimises the cost of achieving a given level of output is that which is cost-effective (Shiell et al. 2002).

The third question is: *"How should these (health) goods, services, and environments be distributed between members of society?"* (Edwards and McIntosh 2019). This question is based on the choice of principles of equity or fairness. Scarcity is the reason economists are interested in equity (the same as applies for efficiency). If resources were not scarce, it would be fair for people to consume as much as they want or need of any particular commodity, including

health care. However, because of scarcity, it has to be judged what a fair allocation might be (Shiell et al. 2002).

2.2.6 The margin

In economic evaluation, it is very important to distinguish between the average and the margin (Goodacre and McCabe 2002). For example, the average cost per unit of output is the total cost divided by the total output, while the marginal cost per unit of output is the cost of the next unit of output. Similarly, the marginal benefit is the additional benefit obtained by consuming the next unit of an output. In an efficient world, marginal cost and marginal benefit are equal for each output, although they may vary across outputs (Zöllner et al. 2003). Economic evaluation is nearly always concerned with the margin rather than the average (Goodacre and McCabe 2002). "Marginal" does not mean small or insignificant. Margin can be illustrated by the following example: the marginal savings associated with a one-day reduction in the length of a hospital stay are typically much lower than the average cost per hospital bed day because of the existence of fixed costs (Shiell et al. 2002).

2.2.7 Incremental analysis

Incremental analysis refers to the process of estimating the additional cost per unit of outcome achieved when comparing one form of treatment to another form of treatment. Incremental cost-effectiveness refers to the difference in cost between the programmes being compared divided by the difference in their outcome (Shiell et al. 2002). Depending on the kind of analysis being conducted (and what kind of outcome is being used), this ratio can be either a cost-effectiveness, a cost-benefit or a cost-utility ratio (Goossens et al. 1999). Types of economic analyses will be covered further in Section 2.5.

2.3 Why do we need economic evaluation?

This section will introduce what ideal market conditions are and then move on to causes of market failure in healthcare. The concept of economic evaluation as a solution to replicating the 'missing market' (due to market failure) will then be introduced.

Under ideal market conditions, production of goods or services is efficient (it is done at the lowest possible cost per unit). Consumption is also efficient: consumers are getting the best value for their money by combining goods and services in a manner that attains them the highest possible satisfaction (maximum utility) given their limited income (Mwachofi and Al-Assaf 2011). Economic efficiency enhances social welfare by ensuring resources are allocated and used in the most productive manner possible (HM Treasury 2018). The condition where there is no waste in production or in consumption is known as Pareto optimality or social efficiency (Mwachofi and Al-Assaf 2011).

Under Pareto optimality it is not possible to make one person better off without making at least one person worse off, and everyone is at their highest possible welfare level given the resources they own (Mwachofi and Al-Assaf 2011). This is an optimal situation. Market failure refers to a situation where market forces alone are not sufficient to deliver a socially efficient allocation of resources / achieve economic efficiency (Edwards and McIntosh 2019). With market failure the market fails to provide the optimal allocation of resources (Edwards and McIntosh 2019).

There are four broad causes of market failure recognised by HM Treasury's The Green Book (HM Treasury 2018, Finch et al. 2020). These are the under-provision of public goods, imperfect information, positive or negative externalities and market power, as shown in Box 2.1.

Box 2.1 Causes of market failure

Under-provision of public goods or services: Where goods or services that benefit the whole of society are under-provided by markets – first, because it is difficult to stop others from using or benefiting from them and, second, because the quantity needed tends not to vary by how many people require them. Examples include defence, clean air, street lighting and preventive services/goods.

Imperfect information about goods and services / information asymmetry: The buyer and seller have different information about a good or service, leading to:

- Adverse selection – for example, individuals in poor health have a greater incentive to purchase health insurance than those in good health. Individuals in poor health make greater utilisation of health care than the healthy, leading to higher pay-outs by the insurance company.
- Moral hazard – for example, when a person's behaviour alters after the risk of their actions is borne by others. Individuals covered by health insurance tend to use more health care and they might not take necessary precautions to stay healthy because they know they have insurance coverage.

Externalities: Where consuming a good or service affects others – either positively or

negatively. Smoking is an example of a negative consumption externality because one individual's consumption (smoking) affects other people's health negatively (effects of second-hand smoke). An example of a positive externality is immunisation. If some individuals are immunised, they provide "herd immunity" in the sense that they do not get the illness therefore they do not pass it on to others.

Market power: A lack of competition renders a market inefficient. For instance, oligopoly (when there are only a few large sellers in the market): the sellers have enough market power to set prices and the market fails to allocate resources efficiently. An example of oligopolies is in the US health insurance industry which is dominated by a few large companies. Another example is a pharmaceutical company that has a patent on a drug. The company is a monopoly because no other company can legally produce and sell that drug until the patent runs out.

Adapted from: (Mwachofi and Al-Assaf 2011, HM Treasury 2018, Finch et al. 2020)

The main reason for market failure in the case of preventive goods and services is that these are often seen as public goods. A good is a public good if one cannot exclude anyone from enjoying it (non-excludability) and the consumption of it does not reduce the amount available for everyone else (non-rivalry in consumption). Once public goods are produced, the producer cannot limit its consumption to paying customers, and the consumption by one individual does not limit consumption by others (Edwards and McIntosh 2019).

It is assumed in markets for normal goods that the consumer is the best judge for his own welfare. However, this is not the case in the market for health care (Edwards and McIntosh 2019). Information asymmetry between providers and consumers is widely recognised as a cause of market failure in health markets (Watts and Segal 2009). In our day-to-day life most choices are made by individuals (consumers) who receive the benefits and incur the costs. They assess the value and the benefits offered by a product and then make a decision about whether they should buy the product using the resources available to them. Yet, this is not the situation in healthcare. In healthcare, because of a lack of medical knowledge the consumers (patients) are typically not aware what type of healthcare is needed, nor what the benefits are likely to be (Drummond et al. 2015). There is a distinctive asymmetry of information between the patient and the clinician. In this case the clinician, who has the expertise to diagnose, advise and to help select alternative courses of action, acts as an agent for the patient. However, a conflict of interests might exist between the clinician and the patient, and/or the clinician may not be best placed to identify and synthesize all evidence and to do the computation

required to fully access the alternative courses of action (Drummond et al. 2015).

Another source of market failure in ill-health prevention is time inconsistent preferences (Suhrcke et al. 2007, Hale et al. 2012). An individual may choose instant gratification over their long-term interests, such that a commitment made in the present to behave in a certain way in the future will be broken when that time in the future comes. For example, it is easy to make a commitment today to start exercising tomorrow; the costs seem low compared to the benefits. However, when tomorrow arrives it becomes the present and the individual is again faced with high "effort" costs relative to the benefit of exercising and can often put off exercising (Edwards and McIntosh 2019).

Departures from rationality may also cause market failure. The assumption that people act rationally (defined as maximising their expected utility) is core to economic thinking. However, it is recognised that children and young people often make choices that may not be in their long-term best interests - they make lifestyle choices with a short-term view, even when they are informed of future consequences (Suhrcke et al. 2007, Hale et al. 2012).

Within market economies, addressing market failure is a key rationale for government intervention (Suhrcke et al. 2007, Finch et al. 2020). Governments intervene through direct provision of healthcare services, including direct funding to public or private bodies for the provision of health services; subsidy to consumers for private health services; or subsidies to consumers for the purchase of private health insurance (Watts and Segal 2009).

A prominent example of a health issue bearing substantial cost to society and reducing social welfare is obesity. People with obesity have an increased likelihood of developing various conditions such as heart disease, stroke, diabetes, musculoskeletal disorders, depression, and cancer. The costs and harms of obesity are not fully taken into account by the market. Food companies set their price in relation to their cost of production and sourcing ingredients, not the subsequent implications for population health. These are negative externalities. Consumers are often unaware of, or do not consider, the longer-

term health consequences of the food and drink they consume meaning that there is imperfect information leading to adverse selection (Finch et al. 2020).

As a result of market failure, the measure of “value” usually obtained by measuring individuals’ responses to price and quantity changes in the typical market is absent and preferences are not revealed in the normal manner. Economic evaluation (EE) is used in order to re-instate the missing market. It reconstructs costs and benefits within a formal evaluative framework to provide information on the ‘worthwhileness’ of particular allocative decisions. It is used as a mean to provide information for making resource allocation decisions in healthcare (McIntosh et al. 2010).

Choice is one of the fundamental concepts in economics, and EE provides vehicles to make appropriate choices (Drummond et al. 2015). In healthcare resources are limited, and it is impossible to produce all desired outputs, hence there is a necessity to make choices. These choices are made on the basis of many criteria, some of them are explicit but some are implicit (Drummond et al. 2015).

In their book, Drummond and colleagues (Drummond et al. 2015) list four reasons for organised EEs: 1) Without systematic analysis, it is difficult to identify the relevant alternatives clearly. 2) The perspective (or viewpoint), assumed in analysis is important. Analytic perspectives may include the following: the individual patient, the specific institution, the target group for specific services, the Ministry of Health budget, the government's overall budget, the wider economy or the aggregation of all perspectives (the societal perspective). 3) Without some attempt at quantification, informal assessment of orders of magnitude can be misleading. The real cost of any programme is not the total programme budget, but rather the value of the benefits achievable in some other programme that has been forgone by committing the resources to the first programme. Economic evaluation seeks to estimate this “opportunity cost” and to compare with programme benefits. 4) Systematic approaches increase the explicitness and accountability in decision-making.

2.4 What is economic evaluation?

According to Drummond and colleagues (2005), economic evaluation (EE) is *"a comparison of two or more alternative courses of action, while considering both inputs (costs) and outputs (consequences) associated with each"* p.22 (Drummond et al. 2005c) The basic tasks of any economic valuation are *"to identify, measure, value, and compare the costs and consequences of the alternatives being considered"* p.4 (Drummond et al. 2015).

Figure 2.1 is a schematic representation of EE components. It illustrates the choice between two alternatives programmes A and B. The general rule, when assessing A and B, is that the difference in costs (between A and B) is compared with the difference in consequences (between A and B), in an incremental analysis.

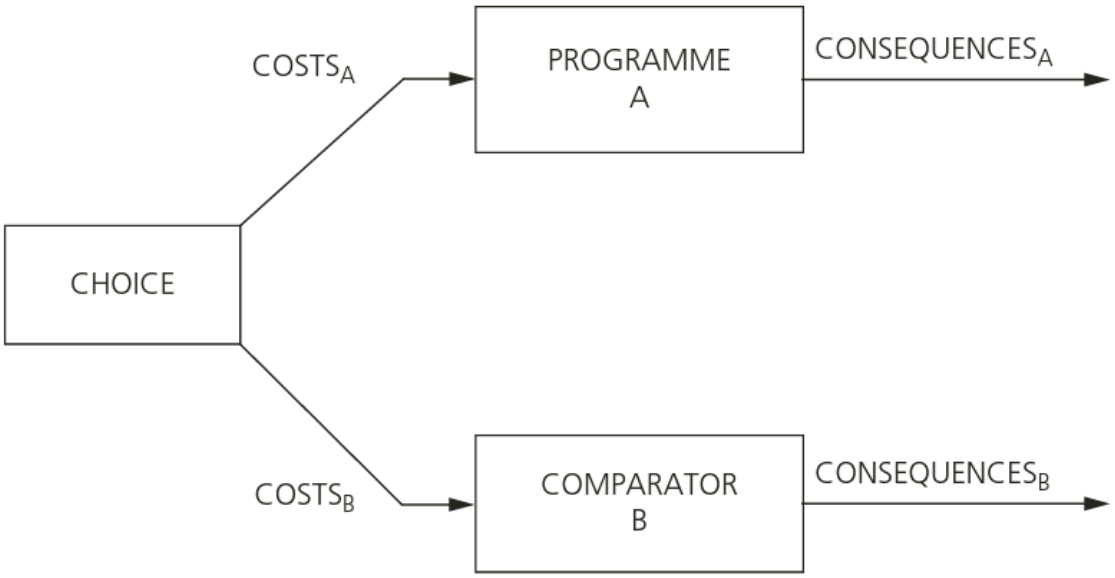

Figure 2.1 Economic evaluation involves comparative analysis of alternative courses of action

Source (Drummond et al. 2015).

EEs aim to answer the following question: *"Are we satisfied that the additional healthcare resources (required to make the procedure, service, or programme available to those who could benefit from it) should be spent in this way rather than some other ways?"* (Drummond et al. 2015)

The choice of comparison intervention is an important factor in economic analysis (Goodacre and McCabe 2002). In relation to healthcare, alternative courses of action refer to the range of ways in which healthcare resources can be used to increase population health. For example, pharmaceutical or surgical interventions, screening or health promotion programmes. Healthcare costs are referred to the value of tangible resources available to the healthcare system. For example, clinical and other staff, capital equipment and buildings, and consumables. Non health service resources are also used to produce healthcare, e.g. the time of patients and their families. Consequences represent all the effects of healthcare programmes other than those on resources. These generally focus on changes in individual's health, which can be positive or negative, but can also include other effects that individuals may value, such as reassurance and information provision (Briggs et al. 2006).

The purpose of EE is to inform decisions in the absence of a normally functioning market. EE *"provides a framework to make best use of clinical evidence through an organised consideration of the effects of all the available alternatives on health, healthcare costs, and other effects that are regarded as valuable"* p.1 (Drummond et al. 2015).

2.5 Economic evaluation frameworks

EE addresses questions of technical and allocative efficiency. Technical efficiency answers the question *"How to?"*, and thus a comparison of programmes within a disease area is required. Cost-effectiveness analysis (CEA) is used to answer this question. Allocative efficiency answers the question *"Whether to?"*, by comparing programmes from different disease areas. Cost-benefit analysis (CBA) and cost-utility analysis (CUA) are used in this case.

Figure 2.2 shows the types of healthcare evaluation approaches by answering two questions: 1) Is there a comparison of two or more alternatives? 2) Are both costs (inputs) and consequences (outputs) of the alternatives examined? (Drummond et al. 2015). Studies with no alternatives compared, are not considered an evaluation, but rather a description of a single service, programme or intervention (cells 1A, 1B and 2). Cells 3A and 3B represent

situations with two or more alternatives compared, but in these cases, the costs and consequences are not examined simultaneously. Only the situation when two or more healthcare alternatives are compared, and both their costs and their consequences are examined is considered to be a full economic evaluation – cell 4. Which type of evaluation might be undertaken will depend on questions of value: Which effects should count? How they should be measured and valued? As well as the question: Which method of analysis might be most useful in different circumstances, and how the results can be interpreted? (Drummond et al. 2015).

Is there a comparison of two or more alternatives?	Are both costs (inputs) and consequences (outputs) of the alternatives examined?		
	NO		YES
NO	Examines only consequences	Examines only costs	2 Partial evaluation Cost-outcome description (an audit of a service or intervention)
	1A Partial evaluation Outcome description	1B Partial evaluation Cost description	
YES	3A Partial evaluation Efficacy or effectiveness evaluation (e.g. randomised controlled trials)	3B Partial evaluation Cost analysis	4 Full economic evaluation Cost-effectiveness analysis Cost-utility analysis Cost-benefit analysis Cost-consequence analysis Cost-minimization analysis

Figure 2.2 Types of healthcare evaluations

Source (Drummond et al. 2015).

Sections 2.5.1 to 2.5.5 below describe various types of full EEs in detail, while their key features are presented in Table 2.1. Full EE types differ only by the outcome measure used. Cost methods are the same for them all (and are covered in Section 2.6).

Table 2.1 Types of economic evaluations and their characteristics

Type of analysis	Health considerations / Other outcomes	Strengths	Important issues
Cost-effectiveness (CEA)	Uses commonly evaluated health outcomes, including clinical or surrogate outcomes (such as blood pressure, renal function).	Relates costs of treatment with therapeutic effectiveness based on health outcomes that are readily available from clinical trials.	The 'cost per unit of health' values obtained in cost-effectiveness analyses can be difficult to interpret; comparisons between populations and diseases are not possible. Effectiveness outcome may not capture all relevant health outcomes.
Cost-utility (CUA)	Health status is transformed into a quality-adjusted life-year score anchored between 0 (death) and 1 (perfect health). All aspects of disease and its treatment are captured in one metric. CUA should be used when health is the sole or predominant benefit of influence (NICE 2012).	The metric comprehensively measures health, enabling benchmarking and comparisons of outcomes among disparate populations and diseases. CUA allows healthcare interventions to be compared so that resources may be allocated more efficiently (NICE 2012).	Cost–utility analyses require the greatest amount of data of all these types of economic evaluation. Assumptions might be required when estimating health-related quality of life. The main disadvantage of CUA is its narrowness, as it measures only health benefits. Also, it accounts only for efficiency and not equity (NICE 2012).
Cost-benefit (CBA)	Health and non-health outcomes are converted into monetary terms. CBA sums the costs and benefits separately to calculate either a net monitory benefit or a benefits to costs ratio. It usually operates with a societal perspective.	If a societal perspective is used, then all costs and benefits should be included. However, if some costs or benefits are not material to the decision, such costs/benefits can be omitted. CBA includes benefits to individuals, as the result of an intervention.	Issues concerning how health and non-health impacts can be valued in monetary terms. Some outcomes, such as equity and social cohesion cannot be quantified readily. CBA may require more data over and above what would be required for a CCA.
Cost-consequences (CCA)	Various outcomes can be considered, not only health: e.g. efficiency (cost per QALY) and equity, adverse events, people's satisfaction with the intervention.	CCA can measure both welfare and quality of life more broadly than CUA.	The outcomes are more difficult to interpret and aggregate that the single CUA outcome. CCA takes more time and resources that CUA (but measures a range of outcomes rather than a single quality of life outcome).
Cost-minimization (CMA)	No difference in health status attributable to disease or treatment strategies is assumed.	Requires minimal data (on costs only) Enables assessment of the technical efficiency of each strategy.	Assumption of identical outcomes of disease and the treatments compared should be robust.

Adapted from (Klarenbach et al. 2014).

2.5.1 Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) is *"an analytic tool in which the costs and effects of a programme and at least one alternative are calculated and presented in a ratio of incremental cost to incremental effect"* (Eichler et al. 2004). CEA address questions of technical efficiency (i.e. the budget is taken as given and the question is "how best" should funds be allocated). Effectiveness units are various health outcomes, such as cases of a disease prevented, hospital days prevented, years of life gained, rather than monetary measures as in cost-benefit analysis (Eichler et al. 2004).

In CEA, the benefits are related to the cost on a unit basis, and the programme yielding the highest unit benefit for unit of resource use is the preferred option (for example, cost per each kilogram of weight loss, or cost per each year of life gained) (Public Health England 2018a). The results of CEAs may be stated either in terms of incremental cost per unit of effect (e.g. cost per life-year gained) or in terms of effects per unit of cost (e.g. life years gained per pound spent) (Drummond et al. 2015).

There are two types of cost-effectiveness ratios: average cost-effectiveness ratio (ACER, Equation 2.1) and incremental cost-effectiveness ratio (ICER, Equation 2.2).

Equation 2.1 Average cost effectiveness ratio (ACER)

$$\textbf{ACER} = \textbf{Cost of intervention / Health effect of intervention} = C_1 / E_1$$

The use of ACER is not recommended because ACERs can be misleading, ignore available alternatives, and fail to maximize net health benefit (O'Day and Campbell 2016). Knowing just the ACERs of two interventions, it is only certain that the intervention with a higher ACER cannot dominate an intervention with a lower ACER. However, the relative costs and benefits of the interventions remain unknown. It is possible that the intervention with a lower ACER: (1) dominates the intervention with the higher ACER, (2) is more costly and more effective, or (3) is less costly and less effective. And if points (2) or (3) are true, the relative magnitude of differences in cost and effectiveness between the

interventions remains unknown (O'Day and Campbell 2016). Therefore, an incremental cost-effectiveness ratio (ICER) is necessary to evaluate the relative costs and benefits between any two competing interventions.

Equation 2.2 Incremental cost-effectiveness ratio (ICER)

$$ICER = \frac{C_1 - C_0}{E_1 - E_0}$$

Where C_1 and E_1 are the cost and health effect of the new intervention, and C_0 and E_0 are the cost and health effect of the comparator.

In reality, choices will likely have to be made between different treatment regimens for the same condition, different dosages or treatment versus prophylaxis, which are mutually exclusive interventions. The key question in this case is: what are the additional benefits to be gained from the new intervention, and at how much greater cost? In order to answer such a question, ICERs are used (Phillips 2009). When the ICER is compared with those of other interventions, or with some notional threshold value which decision-makers are willing to pay for an additional unit of effect, the preferred option from those being evaluated can be established (Briggs et al. 2006). However, comparability of cost-effectiveness ratios is affected by the lack of a single, universally accepted measure of "health gain" (Eichler et al. 2004).

2.5.1.1 Cost-effectiveness outcome measures

CEA outcome measures include clinical outcome parameters (for example, physiological or biochemical, morbidity- or mortality-related parameters). Some examples of these are the number of heart attacks prevented, the number of ulcers prevented, surgical infections avoided, disability days avoided, life-years gained, lives saved, cases detected, asthma-free days, or surrogate endpoints like blood pressure reduction or cholesterol level reduction (Johannesson et al. 1996, Anell and Norinder 2000, Edwards and McIntosh 2019). There are also economically oriented outcome measures, such as hospital days and days off work (Walter and Zehetmayr 2006). Examples of dental health-related outcomes in CEAs are number of carious surfaces/teeth averted, incremental change in dmft/dmfs (decayed, missing and filled teeth / tooth surfaces), teeth saved, and

children saved from caries experience / extraction experience (Anopa et al. 2020).

In case of CEA, the lack of a single generic outcome (such as QALY in CUAs) highlights the need for an extra valuation step to decide whether these outcomes are worth the investment (Edwards and McIntosh 2019). The use of a wide range of outcome measures in CEAs may prevent direct comparisons between interventions (Rogers et al. 2019, Anopa et al. 2020).

2.5.2 Cost-utility analysis

Cost-utility analysis (CUA) is a particular type of CEA that is commonly used in the health sector (Public Health England 2018a). In CUA the effects of different interventions are measured using utility units (e.g. quality-adjusted life years, QALYs). Alternative interventions are then compared in terms of incremental cost per QALY (McIntosh and Luengo-Fernandez 2006). Currently, CUA represent the most widely published form of economic evaluation (Drummond et al. 2015).

The main difference between CEA and CUA is that a CUA typically uses generic preference-weighted health-related quality of life attributes as its outcome measure and therefore outcomes are represented in terms of quality adjusted life years (QALYs) instead of the natural units (as is the case in CEA). CUA can be seen as an improvement on CEA, as it takes account of both quality and quantity of life and facilitates comparability across programmes (Edwards and McIntosh 2019).

Given the need in most healthcare systems to make resource allocation decisions across a whole range of these areas, CUA has increasingly been based on a single generic measure of health. Although other measures have been suggested the QALY is the most frequently used measure for this purpose (Briggs et al. 2006). CUA provides a common unit (cost per QALY) and results in an estimate of the costs of provision of one year of perfect health following an intervention. It therefore helps to quantify the value for money that an intervention provides (Edwards and McIntosh 2019).

2.5.2.1 Quality adjusted life years (QALYs)

QALYs were developed during the 1960s by economists, operational researchers, and psychologists (Edwards and McIntosh 2019) and are the recommended measure of health outcomes in economic evaluations in the United Kingdom (NICE 2012). QALYs are a generic outcome measure. The use of QALYs allow comparisons to be made across interventions, even if they are carried out in different disease/condition areas, unlike the situations when incomparable effectiveness measures (such as different natural health outcome units or disease-specific quality of life measures) are used.

A QALY is an economic outcome that combines preferences for length of survival and quality of life into a single measure (Glick et al. 2014). QALYs are a multiplication of years of life by weights (utility values) ranging from 0 (death) to 1 (perfect health). Utility measurement is on an interval scale, where the same change means the same irrespective of the part of the scale being considered (for example, a change in health from 0.2 to 0.3 is equivalent to a change from 0.8 to 0.9). States worse than death also exist (for example, a terminal illness that causes a lot of pain or immobility), with such states taking a negative value (Whitehead and Ali 2010).

The utility values, or health-related quality of life (HRQoL) weights, are derived from people's preferences for different health states (Public Health England 2018a). They are preference weights, where preference can be equated with value or desirability. The more desirable (more preferred) health states receive greater weight and, therefore, will be favoured in the analysis (Whitehead and Ali 2010).

The QALY concept is illustrated in Figure 2.3. It combines the survival of an individual with their HRQoL. The figure demonstrates the QALYs gained by an individual who received the treatment (higher curve) in comparison with an individual who did not receive the treatment (lower curve). The area under the curve equates to the total QALY value.

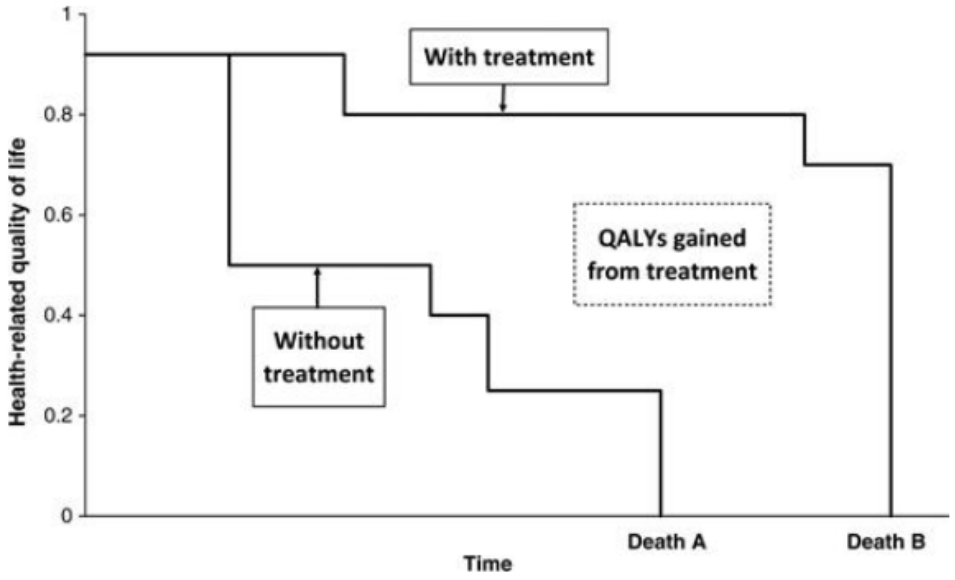

Figure 2.3 QALYs gained from treatment

The lower path shows a hypothetical health profile if no treatment is received; the quality of life of the individual reduces over time, until they die (Death A). If a treatment is received the individual follows the higher path; their quality of life remains at a higher level for longer, in addition to living for longer (Death B). Hence, the total area between the two curves indicates the number of QALYs gained by the treatment. Source: (Whitehead and Ali 2010).

Figure 2.4 is a diagram showing how QALYs are derived from a study with quality of life score values Q0, Q1, Q2 and Q3 collected at each of the study time points T0, T1, T2 and T3 (time measured in years) respectively. QALYs are calculated as the total area under the curve (Curve C), this is the sum of Area K, Area L, and Area M. Equation 2.3 is used to calculate each individual area under the curve (K, L and M).

Area K = (T1 – T0) x (Q0 + Q1) x 0.5

Area L = (T2 – T1) x (Q1 + Q2) x 0.5

Area M = (T3 – T2) x (Q2 + Q3) x 0.5

Equation 2.3 Area under the curve

$$AUC = (t_2 - t_1) \times \frac{(u_1 + u_2)}{2}$$

AUC – area under the curve; t – lengths of time and u – utility / quality of life, at two points in time: 1 and 2.

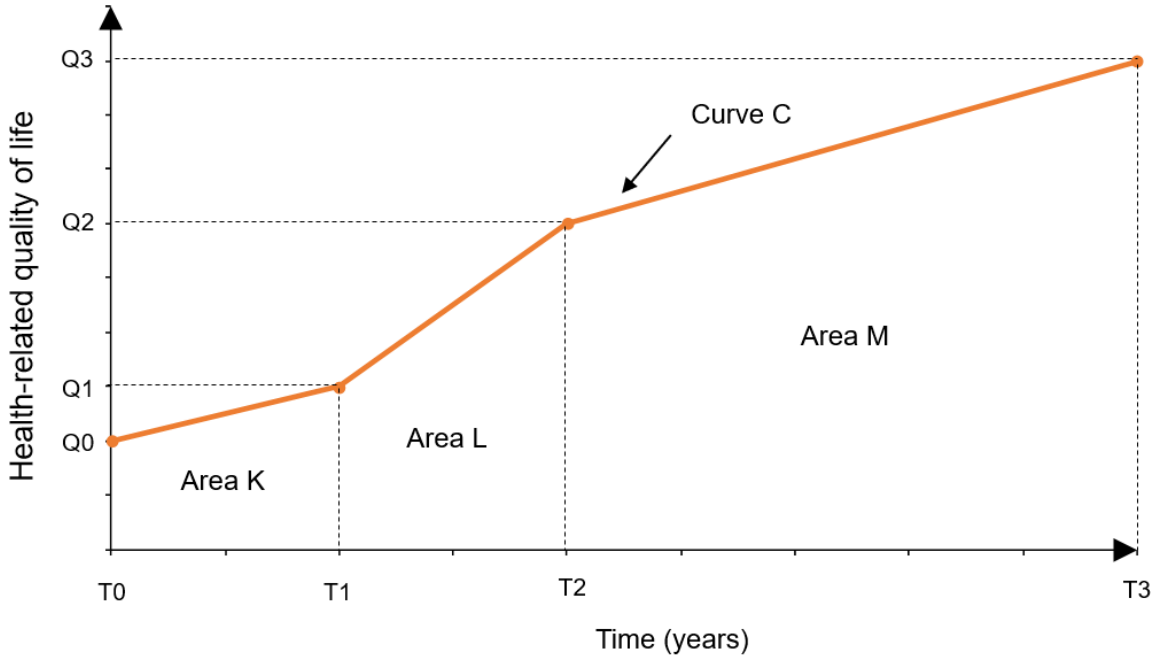

Figure 2.4 QALYs calculation / area under curve illustration

Adapted from (Edwards and McIntosh 2019).

There are two dominant approaches for QALY measurement. The first approach uses pre-scored health state classification instruments and is also called an indirect utility assessment. The second approach directly elicits participants' preferences for their current health (Glick et al. 2014). Pre-scored health state classification instruments are covered in Section 2.5.2.4 Health-related quality of life measures, while the methods of direct preference elicitation, such as the visual analogue scale, standard gamble, time trade off, contingent valuation and conjoint analysis, are covered in Appendix 1.

There are two methods to assess whether an estimate of cost per QALY represent good value for money. These are the QALY league table approach and the threshold approach. Cost per QALY league tables are used to categorise interventions by their average cost per QALY estimate. Such league tables can help to inform decisions as to how a limited amount of money might be efficiently spent in order to achieve the greatest health gain for the population (Edwards and McIntosh 2019). League tables rank alternative healthcare interventions based on their ICERs (Mauskopf et al. 2003). League tables make comparisons possible between interventions in the same disease/therapy area or across therapy areas. QALY league tables have been criticised for oversimplifying complex clinical conditions and for too simplistic resource allocation decisions

(Drummond et al. 1993). Moreover, doubts exist around the value of compiling league tables for cost-effectiveness results for health interventions, primarily due to methodological differences of the included CUA studies (Wilson et al. 2019) and assumptions including choice of comparator, choice of discount rate, time horizon, and population subgroup (Mauskopf et al. 2003).

The threshold approach compares the cost per QALY with a specific threshold value: whether the cost per QALY estimate falls above or below this threshold value. The threshold represents the added cost that has to be borne by the NHS, or wider society in case of PHIs, to forgo one QALY of health through displacement. Interventions above a given threshold value would not be considered good value for money, whereas interventions below the threshold should be accepted (Edwards and McIntosh 2019). In the United Kingdom, NICE has been using a cost-effectiveness threshold ranging from £20,000 to £30,000 per QALY gained since around 2001 (without formal empirical justification, however) (NICE 2013b). Recently there has been an argument that the threshold should be more like £13,000 per QALY (Claxton et al. 2015).

There are exceptions from the standard £20,000 to £30,000 per QALY rule. In 2009 NICE introduced a higher £50,000 per QALY threshold for life-extending treatments for small patient populations at the end of life (NICE 2009). Namely, for treatments that offer an extension to life greater than 3 months compared with current treatment in the NHS, are for patients with a short life expectancy (less than 24 months), and are for small patient populations (not exceeding a total of 7000 patients) (NICE 2009, Thokala et al. 2018). In 2017, NICE adopted a higher threshold of £100,000 to £300,000 per QALY when appraising treatments for very rare diseases (NICE 2017). The greater the QALY gain, the more generous the threshold used when appraising such treatments (Paulden 2017).

2.5.2.2 Disability-adjusted life years (DALY)

Disability-adjusted life years (DALYs) measure the burden of disease in terms of years lost due to Ill-health, disability, or early death and is often used in international comparisons of health and health inequality across countries. DALYs were developed to quantify the burden of disease and disability in

populations, as well as to set priorities for resource allocation (Gold et al. 2002). Total DALYs across a population can be thought of as a measurement of the gap between current health status and an ideal health situation where the entire population lives to an advanced age, free of disease and disability (WHO 2020b). WHO has adopted DALYs as its measure of disease burden. One DALY is one lost year of "healthy" life. Unlike QALYs, which are reported in terms of a QALY gain, DALYs are typically reported as DALYs averted, in order to represent burden (Edwards and McIntosh 2019).

DALYs for a disease or health condition are calculated as the sum of the Years of Life Lost (YLL) due to premature mortality in the population and the Years Lost due to Disability (YLD) for people living with the health condition or its consequences (WHO 2020b).

2.5.2.3 Whose values should be used when measuring child health-related quality of life?

This thesis focuses primarily on child HRQoL measures, as the randomised controlled trial (the Protecting Teeth @ 3 Study), on which one of the empirical segments of this work is based, involved preschool children, aged 3-5 years.

Measuring children's health states is challenging (Prosser 2009, Thorrington and Eames 2015, Hill et al. 2019). Adults, children and adolescents measure HRQoL, perceive and value health differently, hence adult-specific health utilities should not be used in adolescents or young children. Measuring utilities for HRQoL for children and adolescents is a developing field of research (Thorrington and Eames 2015). The methods used to obtain health utilities from adults are well established, but many of these methods have not been validated for use in children and adolescents. NICE recommends the EuroQol 5 Dimensions (EQ-5D) measure as the preferred method for use in CUAs that focus on the adult population, but little specific guidance has been given with regard to an instrument designed for children and adolescents (NICE 2013b). A child-friendly EQ-5D version (EQ-5D-Y) was introduced in 2009 as a more comprehensible instrument suitable for children and adolescents. The recommended age range for the self-complete version of EQ-5D-Y is 8 to 15 years, while for children aged 4-7, the proxy version can be used (EuroQol Group 2020).

Children may lack the cognitive ability to evaluate their health using abstract concepts. Young children may also lack the required linguistic skills to answer questions about their preferences for health using systems designed for self-completion by older children (Thorrington and Eames 2015).

A recent blog post by the Office of Health Economics has highlighted five questions in relation to whether child QALYs equal adult QALYs (Devlin et al. 2020). The authors challenged the assumption that *"a QALY is a QALY is a QALY"*, which implies that a QALY should always "mean" the same thing (i.e. equate to an equivalent and comparable amount of health) regardless of the characteristics of those who happen to be affected by ill health or who benefit from treatment. They posed a question whether QALY gains from health interventions can be directly compared between children and adults. The five questions identified were as follows: 1) What is being measured? (For example, health status or health-related quality of life or quality of life more generally? What aspects of that are most important?) 2) How do children perceive and report their health problems? 3) How should child health be valued? 4) How are the utilities combined with length of life in estimating QALYs for children? and 5) Are QALYs for children "worth more" than adult QALYs?

Devlin and colleagues highlighted that it was crucial that economics researchers working on those challenging questions engaged with decision-makers, to ensure that the way child QALYs were measured and valued was a good "fit" with the principles and social value judgements used in health technology assessment and health policy. They warned that there might not be a "one size fits all" solution, as there would be, for example, differences between various countries (Devlin et al. 2020).

An overview of most widely used child and adolescent preference-based HRQoL measures is presented in Section 2.5.2.4 below, while Chapter 4 comprises a review of instruments for measuring general and oral health-related quality of life in preschool children aged 3-5 years.

2.5.2.4 Health-related quality of life measures

Health-related quality of life HRQoL is a complex, multidimensional concept, including social, emotional and physical functioning or well-being, related to the patient's health state. HRQoL measures can be classified into preference-based and non-preference-based. Preference-based instruments are developed based on classification systems and preferences weights. These preference-based instruments are used in CUAs (Drummond et al. 2005c). HRQoL measures can also be classified into generic and disease specific. Generic HRQoL instruments are designed for different types of disease and different patient populations (Drummond et al. 2005c). These are widely used and have established validity and reliability across different disease conditions and patient populations. Disease-specific HRQoL instruments are designed to assess the quality of life concerning specific diseases, medical conditions, or patient populations (Whitehead and Ali 2010).

Preference-based and non-preference-based HRQoL measures

As mentioned in Section 2.5.2.1, QALYs are based on preference-based outcomes. The measurement of health utilities (HRQoL weights) involves firstly defining health states of interest and then valuing these health states (that is, individuals assess different health states and place a value on each of them). In order to generate HRQoL weights, there are either direct or indirect methods. (Whitehead and Ali 2010). Indirect methods use preference-based measures/instruments, which are discussed in this section, while direct elicitation methods are described in Appendix 1.

The use of preference-based measures/instruments is referred to as "indirect" method of valuing health states. In this case an existing tariff is applied (Thorrington and Eames 2015). Preference-based measures usually comprise a number of domains (or descriptive sets) that patients can use to describe various aspects of their health (for example, limitations in daily activities and mobility, pain and discomfort). These patient-reported values (profile scores) are then converted to a utility score using a selected algorithm. These algorithms are based on surveying the general public's preferences for different combinations

of health states, which is why these measures are referred to as “preference-based” (York Health Economics Consortium 2016c). Preferences are measured by direct valuation techniques such as time trade-off (TTO) and standard gamble (SG) (Thorrington and Eames 2015). This approach is generally used when valuing generic health states (such as the EuroQol’s EQ-5D, Short Form 6 Dimensions (SF-6D) and the Health Utilities Index (HUI) (York Health Economics Consortium 2016c). The EQ-5D, namely, the EQ-5D-3L version, is NICE’s preferred instrument for cost-utility evaluations in healthcare technology assessments (NICE 2013b).

In contrast, non-preference-based measures are not suitable for application in CUA because they do not allow the calculation of utility values and, consequently, QALYs, but rather only provide a HRQoL score (Bulamu et al. 2015). Examples of generic non-preference-based instruments are Short Form 36 (SF-36), Short Form 12 (SF-12) and a child HRQoL instrument the Paediatric Quality of Life Inventory (PedsQL). The majority of disease specific measures are non-preference-based.

Generic and disease specific HRQoL measures

Generic instruments can be used to measure HRQoL in adults, children and adolescents (where appropriate) for a range of conditions, both chronic and acute. Commonly used generic methods include the EQ-5D, Health Utilities Index (HUI) and Short Form 6 dimensions (SF-6D). The advantage of using generic measures in CUAs is that results can be compared across populations, conditions, and for different treatments or interventions (Thorrington and Eames 2015).

Disease-specific methods measure HRQoL with reference to a particular disease or condition, such as the Asthma Control Questionnaire (ACQ) (Juniper et al. 1999), Schizophrenia Quality of Life Scale (SQLS) (Wilkinson et al. 2000), Paediatric Asthma Health Outcome Measure (PAHOM) (Chiou et al. 2005), or Early Child Oral Health Impact Scale (ECOHIS) (Pahel et al. 2007). These are essentially measures of “effectiveness” that are used in CEA. Disease-specific measures can have the benefit of being more sensitive to small changes in the condition of the patient in question (responsiveness to change) (Drummond 2001) and may describe the functioning of a patient with the condition with

greater clarity than a generic classification system that may overlook some aspects of HRQoL, but, on the other hand, utilities calculated using these instruments lack comparability across different diseases (Thorrington and Eames 2015).

Adult generic preference-based HRQoL measures

A review of papers (published on Web of Science in 2004–2010) reported that the most widely used generic preference-based instrument by far was the EuroQol 5 Dimensions (EQ-5D) (Richardson et al. 2014). The EQ-5D descriptive system is measured in five dimensions: mobility, self-care, usual activities, pain/discomfort, and anxiety/depression (EuroQol Group 1990). The original version, the EQ-5D-3L, has three levels of severity for each dimension. EQ-5D has a large number of value sets including a UK value set elicited using the TTO technique with adults. The newer version, the EQ-5D-5L, has five levels for each of the five dimensions. There is a value set for England, but if EQ-5D-5L is used in technology appraisal submissions, NICE currently recommends use of a cross-walk/mapping to the EQ-5D-3L valuation set (Hill et al. 2019, NICE 2019). The EQ-5D-3L is available in more than 160 translated versions, while EQ-5D-5L is available in more than 125 languages (Edwards and McIntosh 2019).

The three most widely used adult instruments – EQ-5D, Health Utility Index version 3 (HUI3) and Short Form 6 Dimensions (SF-6D) – are summarized in Table 2.2.

Table 2.2 Commonly used adult generic preference-based HRQoL measures

Instrument	No. of dimen-sions	Dimensions	No. of severity levels	Country of tariffs	Valuation technique
EuroQol 5 dimensions (3 levels / 5 levels): EQ-5D-3L (Dolan 1997) / EQ-5D-5L (Herdman et al. 2011)	5	Anxiety/depression, mobility, pain/discomfort, self-care, usual activities	3 / 5	3L: UK, US, plus 16 others 5L: UK plus others	3L: ranking, TTO, VAS, 5L: TTO, DCE
Health Utility Index version 3 (HUI3) (Feeny et al. 2002)	8	Ambulation, cognition, dexterity, emotion, hearing, pain, speech, vision	5–6	Canada, France	VAS transformed into SG
Short Form 6 dimensions (SF-6D) (Brazier et al. 2002)	6	Energy, mental health, pain, physical functioning, role limitation, social functioning	4–6	UK and 5 others	SG, ranking

TTO – time trade-off, VAS – visual analogue scale, DCE – discrete choice experiment, SG - standard gamble. Adapted from (Brazier et al. 2017).

Child and adolescent generic preference-based HRQoL measures

The evaluation of technologies for children and adolescents presents particular methodological challenges, and one of these challenges is in the assessment of their HRQoL. Children and adolescents may be less able to report or assess their own health or the impact of their condition on aspects of their health-related quality of life, and this may require proxy-report and/or self-report of their health according to what is appropriate for their age and cognition (Hill et al. 2019).

There has been a rise in the use of child self-report and proxy-report instruments in paediatric clinical trials within the last decade (Germain et al. 2019). There is a consensus that child self-report should always be used where possible, however, proxy reports are considered to be a valuable way of obtaining information about children whose age or cognitive/health status prevents them from self-reporting reliably. Proxy respondents include the child's parents, clinicians and teachers. Parents are deemed to be the most useful proxies as they are the most familiar with their child's health and life (Thorrington and Eames 2015). Children under the age of five cannot provide reliable self-reports, and for them proxy reports should be used (Wallander et

al. 2001, Varni et al. 2007, Matza et al. 2013). However, there are a number of issues surrounding proxy reports (Germain et al. 2019): for example, parents may misjudge the health of their child owing to their own anxiety during the illness (Thompson et al. 1992, Dahlquist et al. 1994), and studies have shown differences between parent and child ratings for the child's health (Thorrington and Eames 2015).

Some methods have been developed for use exclusively in children and adolescents, and some existing adult-specific methods have been modified to make them child-friendly (Thorrington and Eames 2015). The EQ-5D has a 'youth' version where the questions for each dimension of health are easier to read and more accessible to children, the EQ-5D-Y (Wille et al. 2010b). However, EQ-5D-Y uses the same utility weights in each dimension as the adult version, so does not yet incorporate child and adolescent preferences for health states. Adult preferences for health states may be different from the preferences of children and adolescents and the dimensions included may not cover all dimensions of health relevant to children and adolescents (Keren et al. 2004).

The EQ-5D-Y descriptive system is almost identical to the adult version, comprising of five dimensions: mobility; looking after myself; doing usual activities; having pain or discomfort; feeling worried, sad or unhappy (Ravens-Sieberer et al. 2010). These are the same dimensions of the adult EQ-5D, which were reworded to ensure relevance and clarity for children and adolescents, and each dimension has three levels (Wille et al. 2010a). The EQ-5D-Y can be completed by a proxy (for example, a parent or carer) for children aged 4–7 years and can be self-reported for those aged 8–11 years. Between ages 12–16 the youth or adult versions can be used, and from 16 onwards the adult version is generally preferred (Wille et al. 2010a). There is no EQ-5D-Y UK value set and though it is possible to use the EQ-5D value set by applying the tariff to the analogous domains and levels, there are limitations associated with this approach (Kind et al. 2015, Hill et al. 2019).

A systematic review that aimed to evaluate the use of all direct and indirect methods used to estimate health utilities in both children and adolescents

(Thorrington and Eames 2015), revealed that the most widely used child and adolescents QoL instruments were: EQ-5D, HUI and, to a much lesser extent, EQ-5D-Y and the Short Form (SF).

Health Utilities Index (HUI)

The Health Utilities Index (HUI) is a preference-based measure originally developed for use in children with cancer, although it is more widely regarded and used as a generic preference-based measure (Hill et al. 2019). The HUI consists of two systems, HUI2 and HUI3, both of which can be used for children and adolescents. The HUI2 descriptive system comprises the following seven dimensions: sensation; mobility; emotion; cognition; self-care; pain; and fertility and each dimension has between three and five response levels (Torrance et al. 1996). The HUI3 has eight dimensions: vision; hearing; speech; ambulation; dexterity; emotion; cognition; pain. Each dimension has between five and six levels (Feeny et al. 2002). HUI2 has a UK value set (McCabe et al. 2005) and a Canadian value set, while the HUI3 has a Canadian value set (Hill et al. 2019). The questionnaires are appropriate for a broad range of subjects starting from five years of age. For ages 5-8 years proxy assessment is recommended (by parents/carers). For ages 8-12 years the interviewer administered self-assessment version is recommended, and for individuals 13 years and older self-assessment is appropriate (Brazier and Longworth 2011, Edwards and McIntosh 2019).

Short Form family of HRQoL measures

The Short Form family of HRQoL measures consists of three instruments SF-36, SF-12 and SF-8. These instruments are health profiles consisting of eight scales: physical functioning, physical role, pain, general health, vitality, social function, emotional role, and mental health, and can be used in individuals aged 14 and older. SF-12 is a shorter version of the SF-36. This questionnaire has the same eight scales as in SF-36, however the number of questions referring to each scale has been reduced. SF-8 is an even more reduced version of the SF36. It uses a single item to measure each of the eight domains of health (Edwards and McIntosh 2019). Although these instruments are non-preference based, a

separately developed preference-based instrument, the Short Form 6 Dimensions (SF-6D) (Brazier et al. 2002), provides a means for using the SF-36 and SF-12 in economic evaluation by estimating a preference-based single index measure for health from these data using general population values. The SF-6D allows the analyst to obtain QALYs from the SF-36 for use in cost-utility analyses. Any patient who completes the SF-36 or the SF-12 can be uniquely classified according to the SF-6D (The University of Sheffield 2020).

Child Health Utility 9 Dimensions (CHU9D)

There is also a more recently developed instrument, the Child Health Utility 9 Dimensions (CHU9D), which has been developed in the UK specifically for use in children (Stevens 2009, Stevens 2011, Stevens 2012). The CHU9D has nine dimensions, with five levels each. This instrument was developed with children to assess the child/adolescent's functioning across the health domains of worry, sadness, pain, tiredness, annoyance, school, sleep, daily routine and activities. It was designed for use in children aged 7–11 years, but can be completed via parent/guardian proxy for children aged 4-7 years. Value sets exists for the UK (Stevens 2012), Australia and the Netherlands (Hill et al. 2019). The UK value sets were generated using standard gamble with adult general population (Stevens 2012).

Chapter 4 of this thesis contains a review of instruments for measuring general and oral health-related quality of life in preschool children aged 3-5 years, where such instruments, including CHU9D, are covered in detail.

2.5.3 Cost-benefit analysis

Moving on from the CUA framework and the need for preference-based utility, the cost-benefit analysis (CBA) framework converts all benefits and costs that can be readily quantified into monetary terms. CBA sums the costs and benefits separately to arrive at either a net monetary benefit or a ratio of benefits to costs and consequently it usually operates with a societal perspective (NICE 2012). Besides the evaluation of healthcare interventions, CBA is extensively

used in environmental economics and land use evaluation (Johannesson and Jönsson 1991).

When choosing between interventions, two CBA approaches are commonly used: a) The benefit to cost ratio approach, where projects are compared on the basis of the return to resources employed, or the average benefit per unit cost. The project with the greater ratio of benefits to costs is selected (Birch and Donaldson 1987); and b) The net-benefit approach, where projects are compared on the basis of the excess of benefits over costs (each project's benefits minus this project's costs). Under this approach the higher cost option is chosen only if the additional (marginal) benefits of the higher cost option exceed the additional (marginal) cost of that option (Birch and Donaldson 1987).

The advantages of using CBA include: a) if it is society's interests we are interested in, then all costs and all benefits should be included; b) CBA includes benefits to individuals, such as those of a person being employed (compared with not being employed) as the result of an intervention; and c) expressing costs and benefits in money terms avoids the difficulties of aggregating data that occur with cost–consequences analysis (NICE 2012).

However, there are some disadvantages to CBA, such as: a) some outcomes cannot readily be quantified in monetary terms; b) if decisions are being made about what a government department (or local government) should pay for, then only the costs and benefits of interest to that sector might be required; c) CBA may sometimes have large data requirements (over and above what would be required for other types of evaluations, such as CCA): for example, a survey to estimate "willingness to pay" (WTP) and appropriate estimates of all relevant costs; d) WTP is a measure of demand rather than of need, whereas in the UK's National Health Service (NHS), healthcare is allocated according to need (this may cause contradictions with equity objectives); e) there are measurement issues concerning how health and non-health impacts can be valued in terms of money (NICE 2012).

The methods for valuing benefits in monetary terms in CBA are described in Appendix 2.

2.5.4 Cost-consequence analysis

Cost-consequence analysis (CCA) is a form of EE where disaggregated costs and a range of outcomes are presented to allow decision-makers to form their own opinion on relevance and relative importance to their decision making context (Drummond et al. 2005c). This is usually done using a clear descriptive table to present the effectiveness results (both primary and secondary outcomes) in a disaggregated format, together with the estimates of the mean costs with appropriate measures of dispersion associated with each intervention (Hunter and Shearer 2019). In the case of CCA, all impacts and costs are considered, even if the impacts cannot be costed, when deciding which interventions represent the best value. This type of analysis provides a "balance sheet" of outcomes that decision-makers can weigh up against the costs of an intervention (NICE 2013b). CCA enables decision-makers to consider the outcomes most relevant to them (Edwards and McIntosh 2019). CCA descriptive summary results are often easier to interpret for decision-makers than CEA, CUA or CBA results. In the United Kingdom, NICE has recommended CCA in addition to CUA for evaluating public health interventions (PHIs) (NICE 2012).

CCA is sometimes referred to as a disaggregated approach because the benefits and costs are not combined in a single ratio such as ICER in CUA, cost-benefit ratio in CBA, or in financial terms. A drawback of CCA is that it doesn't provide guidance as to how the different outcomes in the balance sheet should be weighed against each other. When some outcomes show benefits and others show disbenefits, it becomes necessary to consider the relative value of these outcomes (Edwards and McIntosh 2019).

2.5.5 Cost minimisation analysis

Cost minimisation analysis (CMA) is a method of comparing the costs of alternative interventions, which are known, or assumed, to have an equivalent medical effect. This type of analysis can be used to determine which of the treatment alternatives provides the least expensive way of achieving a specific health outcome for a population (York Health Economics Consortium 2016b). CMA is thought to be of limited use outside of pharmacoeconomics (Briggs and O'Brien 2001). In their paper titled *The Death of Cost-minimization Analysis?*

Briggs and O'Brien argue that CMA is an appropriate method of analysis only in rare specific circumstances. The central focus of their discussion is how analysts determine whether programmes have “the same” outcomes under uncertainty. The authors argue that, since “absence of evidence is not evidence of absence”, unless a study has been specifically designed to show the equivalence of treatments (in terms of costs or effects), it would be inappropriate to conduct CMA on the basis of an observed lack of significance in the effect differences between treatments. Instead, analysts should focus their attention on estimation of cost-effectiveness rather than on hypothesis testing of cost or effect differences (Briggs and O'Brien 2001).

2.5.6 Return on investment

Return on investment (ROI) is an economic measure used to indicate how much economic benefit is derived from a program in relation to its costs (Brousselle et al. 2016). It comes from the economics literature of project appraisal and is closely related to cost-benefit analysis (Buck 2018). ROI seeks to compare the cost and benefits of alternative actions to see whether the returns are worth the costs of intervening. There are two different ways that ROI can be calculated (Public Health England 2017): a) as a ratio of the total discounted benefits divided by the total discounted costs; and b) it can also be calculated as total net discounted benefits minus total discounted costs, divided by total discounted costs.

The strengths and weaknesses of the ROI methodology were the focus of several publications (Pokhrel 2015, Brousselle et al. 2016, Buck 2018, Ferguson 2018). The main strength of ROI models lies in its simplicity, allowing decision makers to simulate various investment packages by testing different policy options (Pokhrel 2015). ROI can easily be used to compare investment priorities, namely, the intervention with higher ROI get priority over the ones with lower RRs. This, for example, would allow public health decision makers to use ROI modelling to make their business cases explicit, either for investment or disinvestment. ROI can help to advocate for public health interventions that have long term implications and require substantial investments, by providing robust arguments in their defence (Brousselle et al. 2016). In addition, the process of development

of ROI tools may provide platforms for meaningful engagement of multiple stakeholders and representation of stakeholder benefits in ways that are unique to the stakeholders themselves (Banke-Thomas et al. 2015).

On the other hand, the weaknesses and risks of the ROI have also been acknowledged. ROI only accounts for monetary value – which is derived from market prices – and it has limitations in accounting for externalities and for investments advancing the public good (Hamelmann et al. 2017). It is difficult to attach financial values to "soft outcomes" and to establish what would have happened without the intervention, the counterfactual (Banke-Thomas et al. 2015). There are important concerns related to the way ROIs are calculated, specifically in case of complex public health interventions, which effects are sometimes scattered and intangible (for example, increased well-being or empowerment) and with externalities that are neither easily quantifiable nor easily convertible into monetary terms (Brousselle et al. 2016).

It is often hard to compare ROI ratios across interventions and/or make appropriate conclusions. For instance, if previous ROI modelling showed that the ROI of water fluoridation is twice that of early education programs, does it mean that water fluoridation should have priority over early education (Brousselle et al. 2016)? If allocation decisions were based on ROI only, would it mean interventions with the lowest ROIs should not be funded?

The cost-effectiveness and ROI ratios of public health interventions are discussed further in this chapter in Section 2.10.2.

2.6 Cost data for economic evaluation

2.6.1 Economic evaluation perspectives

Consideration of which perspective should be used is very important before starting any economic evaluation (Edwards and McIntosh 2019). The perspective describes the point of view from which costs and benefits are collected and assessed (Graf von der Schulenburg et al. 2008). The perspective is often selected depending on the purpose of the evaluation, and on which costs and outcomes are relevant to this evaluation. For health technology appraisals NICE

recommends the use of an NHS and personal social services-only perspective (NICE 2013b), however, a public sector perspective is recommended for public health interventions (PHIs) (NICE 2012), as PHIs are complex and target several different stakeholders and outcomes at a time. Public sector perspective includes the health care payer perspective (the NHS perspective in the United Kingdom), personal social services, and local government. PHIs may also be evaluated using a societal perspective. The societal perspective encompasses direct, indirect, and intangible costs, and is even broader than the public sector perspectives (Edwards and McIntosh 2019). Types of costs are explained in detail in Section 2.6.2.

Employer and patient/client perspectives are less commonly used in EEs. The employer perspective includes direct costs and indirect costs such as loss of productivity due to illness. The patient/client perspective includes direct, indirect and intangible costs but is focused more narrowly on the individuals directly affected by an intervention rather than on population-level effects (Edwards and McIntosh 2019).

The broader the perspective, the more challenging is the task of identifying and measuring resource use across multiple agencies. The benefit of a wider perspective is transparency, as cost cannot be “shifted” into other sectors to make an initiative appear more favourable. However, conducting an EE using a broader perspective is time and resource intense, hence, time and funding constraints may prevent a broad perspective being used (Edwards and McIntosh 2019).

The type of the economic evaluation framework used may also influence the choice of perspective. CEAs generally take a public sector perspective, while CBAs take a societal perspective. CCA usually also take a societal perspective and are useful for complex PHIs because they present costs and consequences in disaggregated form, therefore decision-makers are able to assess the impact of an intervention on health and non-health outcomes across sectors (Edwards and McIntosh 2019).

2.6.2 Cost types

Whenever any type of full EE approaches is used, both the costs and benefits of competing interventions need to be evaluated. Identifying, measuring and costing the resources used for each option is one of the first steps of an EE (Edwards and McIntosh 2019). The categories of costs with examples from a clinical setting (GP) and a non-clinical setting (school) are summarised in Table 2.3.

Table 2.3 Summary of the categories of costs with examples from a clinical setting and a non-clinical setting

Type of cost	Description	Clinical setting example (GP clinic)	Non-clinical setting example (school)
Direct	Costs that are directly associated with the programme under evaluation (e.g. staff salaries, equipment, capital and overhead costs of running a programme). Can be medical (e.g. drugs, physician or hospital services) or non-medical (e.g. transportation cost, care provided by family members). Can be incurred by the service provider, but also can be incurred by the person receiving treatment (e.g. out of pocket expenses).	Staff costs (both monetary and opportunity costs) for a nurse to deliver a smoking cessation service.	Teacher time (both monetary and opportunity cost) to deliver an anti-bullying intervention.
Indirect (productivity loss)	Costs that are associated with the programme under evaluation but are not directly attributable (e.g. lost wages due to missing work, income forgone due to a premature death).	Loss of earnings for the individual to attend the smoking cessation service appointment during working hours.	Parental loss of wages to meet with school to discuss bullying incidents.
Intangible	Costs that are associated with concepts that are difficult to quantify and measure (e.g. pain, anxiety, suffering, grief, social stigma).	Cravings during first few days of nicotine withdrawal.	Emotional distress of child who is being bullied.
Marginal	Costs of providing one more unit of a good or service.	Treating one additional person at the smoking cessation service.	Rolling out the anti-bullying intervention to an additional year group in the school.

Incremental	Additional costs incurred by one service compared to another.	The additional cost of providing the smoking cessation service by a nurse compared to providing the service through a smoking cessation leaflet service.	The additional cost of providing the anti-bullying intervention by a schoolteacher compared to providing the intervention through a mobile phone app or other online service.

Adapted from (Edwards and McIntosh 2019).

In addition to the information presented in Table 2.3, direct costs can be classified further into fixed, semi-fixed, and variable costs (Edwards and McIntosh 2019). Fixed costs are usually the capital and overhead costs for a programme. They do not depend on the level of activity and will be incurred whether a person attends their appointment or not (for example, heating and lighting for the building). Semi-fixed costs include staffing costs (they are fixed to a certain degree, but if extra staff are employed to deal with higher than expected attendance rates the cost of providing the service increases). Variable costs change proportionally with the volume of activity (for example, drugs, consumables, fuel) (WHO 2020a). There are also stepped costs: they have the same behaviour as the fixed costs until the level of activity reaches a threshold, when they step to a higher level. For example, a doctor can treat a certain number of patients, if this number is exceeded another doctor has to be hired, the cost of labour jumps when the threshold has been surpassed (WHO 2020a). Total cost is the sum of fixed, variable, semi-variable and stepped costs for a certain volume of activity.

Assessments should make clear whether average costs or marginal costs are being used in the analysis. Average cost analysis considers the total (or absolute) costs and outcomes of an intervention, marginal cost analysis considers how outcomes change with changes in costs (for example, relative to the standard of care or another comparator). Marginal cost analysis may reveal that, beyond a certain level of spending, the additional benefits are no longer worth the additional costs (NICHSR 2020). Due to diminishing returns, the marginal cost of producing an additional unit increases at higher levels of output. In economics, the optimal level to produce a good or service occurs at the point where the marginal cost is equal to the marginal revenue/benefit. This is where the total profit is maximised (Edwards and McIntosh 2019).

2.6.3 Costing approaches

It is generally accepted that costing approaches should be the same regardless of the EE technique used: CEA, CUA or CBA (McIntosh et al. 2010). Costing can be conducted as either a top-down or bottom-up approach. A top-down approach uses total costs generated through information about budgets for the delivery of a programme (overheads, administration, staff cost, and consumables) to produce an average cost per person. The advantage of this approach is that it requires less resource intensive data collection, but the disadvantage is that it doesn't consider variation, a top-down costing of participants resource use assumes that all people have used resources equally. On the other hand, a bottom-up approach uses individual level data to calculate total costs (also called micro-costing). This approach is more resource-intensive on the part of the researcher, however, the richer data will allow analysis of the variation between individuals and settings. Individual level resource use data can be measured in two ways: a) by asking the person (or their proxy) to recall their frequency and duration of contacts with relevant health and social care services during a given period; and b) extracting routinely collected information from health and social care databases, as well as using linked databases (Edwards and McIntosh 2019). When measuring individual level resource use data, the balance between the quantity of information requested and the participant’s burden of completing questionnaires should be considered. Obtaining resource use information from routinely collected health and social care data removes the burden from participants. In this case, however, participants consent is required to access their personal data (Edwards and McIntosh 2019).

2.7 Technical issues in economic evaluation

This section presents various technical aspects of economic evaluation in healthcare, such as the time horizon and discounting, uncertainty, and missing data.

2.7.1 Time horizon and discounting

Time is an important aspect of health economic evaluation, as the timing and duration of clinical events, healthcare interventions and their consequences all

affect estimated costs and effects (O'Mahony et al. 2015). According to the York Health Economics Consortium's health economic terms glossary, "the time horizon used for an economic evaluation is the duration over which health outcomes and costs are calculated" (York Health Economics Consortium 2016d). It is recommended that resource use data are measured for as long as effects relating to the intervention are present. However, this is not always practical, especially for PHIs that are expected to acquire benefits over a long-term period (Edwards and McIntosh 2019). NICE guidance suggests that a time horizon of less than a lifetime can be justified if there is no differential mortality effect between the intervention and control groups, and if the differences in costs and other outcomes relate to a shorter period (NICE 2012). NICE also states that "the time horizon should be chosen so as to incorporate all important costs and effects" (NICE 2012). Longer time horizons are applicable to chronic conditions associated with on-going medical management, rather than a cure. A shorter time horizon may be appropriate for some conditions or interventions, for which long-term consequences are less important. The same time horizon should be used for both costs and health outcomes (York Health Economics Consortium 2016d).

When cost and effect are incurred at substantially different times these differences in timing must be accounted for (Glick et al. 2014). There are two main adjustments that must be considered: inflation for costs and time preference for cost and effect. Inflation refers to the general upward price movement of goods and services overtime. Time preference, or discounting, refers to people's differential valuation of a good or service, depending upon when the good or service is consumed (Glick et al. 2014). People tend to have a positive rate of time preference (Edwards and McIntosh 2019). For instance, being given £100 today is valued more highly than being given £100 in five years' time. Due to the presence of inflation and time preference cost and effect in different time periods are not directly compatible. Comparison requires conversion to a common time period, for example, the first year of the trial or the year the trial results will be reported (Glick et al. 2014).

Discounting is used to express costs occurring in the future (future value) in present day values using Equation 2.4.

Equation 2.4 Discounting

$$PV = \frac{FV}{(1+i)^n}$$

where PV is present value, FV - future value, i - the discount rate, n - time period.

In the UK, generally, the same annual discount rate of 3.5% should be used for both costs and benefits for the reference case, while the rate of 1.5% is recommended to be used in sensitivity analyses (NICE 2013b). However, since PHIs usually act over a long term and have effects lasting for many years, in this case, NICE conversely recommends using a discount rate of 1.5% for all costs and benefits for the base-case scenario, and using a higher 3.5% discount rate on both costs and benefits in sensitivity analyses (NICE 2012).

2.7.2 Uncertainty

Historically, uncertainty in economic evaluation was handled using simple one-way sensitivity analysis methods, where individual parameters of an analysis were varied one-by-one (while holding all other parameters constant) over a range of values. However, within the last two or three decades, with the increasing use of the clinical trial as a vehicle for economic evaluation, there has been increasing interest in the use of statistical methods for handling uncertainty in patient-level data on both costs and effects (Briggs 2004).

There are several types of uncertainty in economic evaluation. Types of uncertainty in modelling are described in Table 2.4.

Table 2.4 Uncertainty for decision modelling: Concepts and terminology

Preferred term	Concept	Other terms sometimes employed	Analogous concept in regression
Stochastic uncertainty	Random variability in outcomes between identical patients	Variability Monte Carlo error First-order uncertainty	Error term
Parameter uncertainty	The uncertainty in estimation of the parameter of interest	Second-order uncertainty	Standard error of the estimate
Heterogeneity	The variability between patients that can be attributed to characteristics of those patients	Variability Observed or explained heterogeneity	Beta coefficients (or the extent to which the dependent variable varies by patient characteristics)
Structural uncertainty	The assumptions inherent in the decision model	Model uncertainty	The form of the regression model (e.g., linear, log-linear)

Source: (Briggs et al. 2012).

Sensitivity analyses can be deterministic or probabilistic. In a deterministic sensitivity analysis, parameter values are varied manually to test the sensitivity of the model's results to specific parameters or sets of parameters. In a probabilistic sensitivity analysis, all parameters are varied simultaneously, with multiple sets of parameter values being sampled from a priori defined probability distributions (for example, bootstrapping techniques or Monte Carlo simulations might be used). The outputs from a probabilistic sensitivity analysis may inform several different forms of analysis, including confidence intervals, cost-effectiveness planes, and cost-effectiveness acceptability curves (Briggs et al. 2012).

2.7.3 Missing data

Incomplete data are inevitable in economic analysis conducted alongside clinical trials (Glick et al. 2014). Cost and effect data may be incomplete due to item level missingness. For example, data for visit 3 might be missing, but data for visits 1, 2 and 4 are available. Cost/effect data may also be incomplete due to loss to follow-up: for example, data for visits 1 and 2 are available but all data

after visit 2 are missing. This type of data are called censored (Glick et al. 2014).

In the past, the most commonly used methods for analysing datasets with incomplete observations were relatively ad hoc (for example, case deletion - ignoring subjects with incomplete information, or mean imputation - substituting the missing values with single estimates) and suffered from potential limitations. More recently, several alternative and more sophisticated approaches (for example, multiple imputation) have been proposed that attempt to correct the flaws of the simple imputation methods (Manca and Palmer 2005).

According to Little and Rubin there are three types of missing data (Little and Rubin 2019):

a) Missing completely at random (MCAR), occurs when the reason for the missing data is independent of the mechanism that generates the data. It implies that, for example, the cost for participants who have incomplete follow-up is the same, except for random variation, as the cost for participants with complete data (Glick et al. 2014). In case of MCAR, incomplete observations are missing for reasons unrelated to the data, and the complete cases are fully representative of the cases in the original sample.

b) Missing at random (MAR), where the probability of observing y at time t depends on the value of the same variable in the previous period, but not on unobserved variables at time t. Missing observations are fully predictable from the variables in the dataset.

c) Missing not at random (MNAR), in which the value of missing response y at time t depends on some unobservable variable(s) at time t. This is also called non-ignorable non-response.

A correct identification of the missing data mechanism is fundamental to the choice of the approach to be used to handle the problem (Manca and Palmer 2005).

2.8 Reporting and presentation of economic evaluation results

This section will cover the means used for efficient reporting of EE results, such as the cost-effectiveness plane and cost-effectiveness acceptability curve, as well as describe the checklists used for EE reporting and the evaluation of the quality of EEs.

2.8.1 Cost-effectiveness plane and cost-effectiveness acceptability curve

The cost-effectiveness plane is used to visualize the differences in costs and health outcomes between the intervention and the comparator in two dimensions, by plotting the costs against effects on a graph (Figure 2.5). It is usually used to present CUA results. Health outcomes (or effects) are usually plotted on the x-axis and costs on the y-axis. More than two points can be represented on the plane, with the line connecting cost-effective alternatives being called the cost-effectiveness frontier. Cost-effectiveness planes are also useful to show the uncertainty around cost-effectiveness outcomes, often represented as a cloud of points on the plane corresponding to different iterations of an economic model in a (probabilistic) sensitivity analysis (York Health Economics Consortium 2016a).

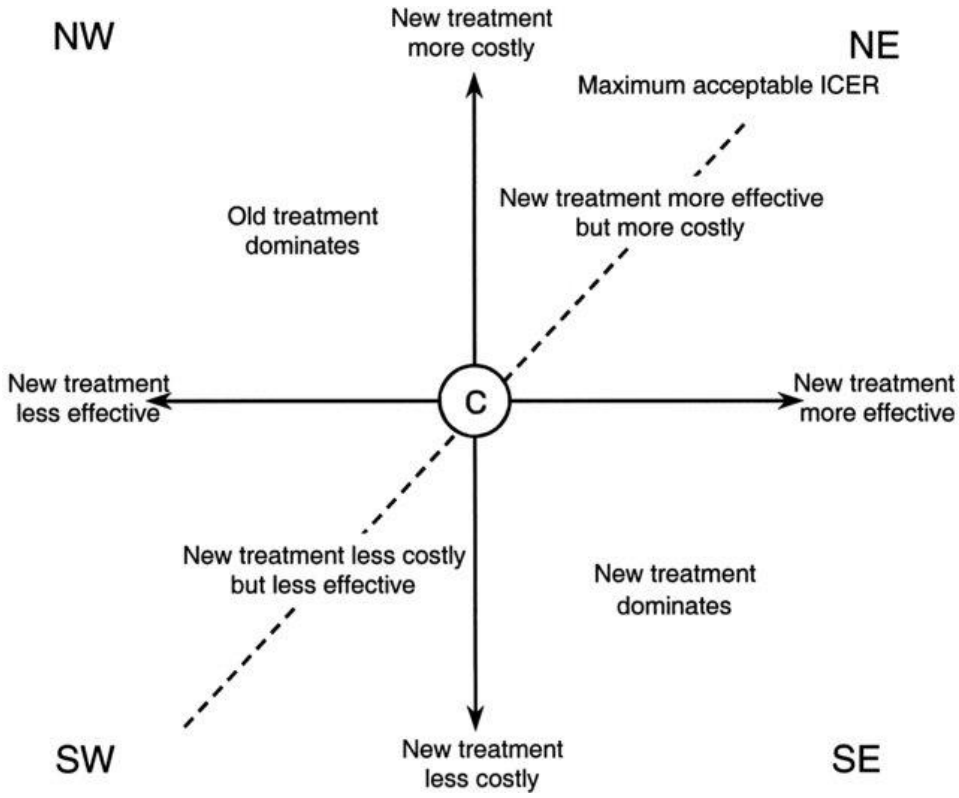

Figure 2.5 Decision rules and the cost-effectiveness plane

Note: The origin (C) is the current/old treatment. The dotted line is the maximum willingness to pay threshold, the maximum acceptable ICER (incremental cost effectiveness ratio). Quadrants: NW – north-west; NE – north-east; SE – south-east; SW – south-west.
Source: (Briggs and Tambour 2001)

The cost-effectiveness plane is divided into four quadrants, as is shown in Figure 2.5 and Box 2.2. Often, CUAs/CEAs deliver results in the north-east (NE) quadrant, in which new interventions generate more health gains but are also more expensive.

Box 2.2 Four quadrants of the cost-effectiveness plane

- ✓ **South-east (SE) quadrant: $C_1 – C_0 < 0$ and $E_1 – E_0 > 0$;** new treatment dominates – accept new treatment as it is both cheaper and more effective than the existing therapy.
- ✓ **North-west (NW) quadrant: $C_1 – C_0 > 0$; $E_1 – E_0 < 0$;** old treatment dominates – reject new treatment as it is both more expensive and less effective than the existing therapy.
- ✓ **North-east (NE) quadrant: $C_1 – C_0 > 0$; $E_1 – E_0 > 0$;** trade-off – consider the magnitude of the additional cost of the new therapy relative to its additional effectiveness.
- ✓ **South-west (SW) quadrant: $C_1 – C_0 < 0$; $E_1 – E_0 < 0$;** trade-off – consider the magnitude of the cost-saving of the new therapy relative to its reduced effectiveness.

Where C_1 and E_1 are the cost and health effect of the new intervention, and C_0 and E_0 are the cost and health effect of the comparator.

Adapted from (Briggs and Tambour 2001).

Where one intervention is simultaneously cheaper and more effective than the other (SE and NW quadrants), there is a clear treatment of choice, since one treatment dominates the alternative (Briggs and Tambour 2001). However, NE quadrant, where the new intervention is more effective and more costly, and SW quadrant, where new intervention is less effective and cost-saving, are the trade-off quadrants. When a new intervention falls into either of these quadrants the adoption of the new intervention will be determined using a cost-effectiveness threshold with regards to whether it is value for money compared to the current standard of care. The cost effectiveness threshold, often referred to as the "willingness to pay threshold", represents the maximum amount of money that the decision-maker (for example, the NHS) is willing to spend in order to achieve one unit improvement in outcome (for example, to gain one QALY) (Edwards and McIntosh 2019). In the United Kingdom, the threshold of £20,000 - £30,000 per QALY is used (NICE 2013b). This threshold value of the ICER can be represented by the dashed line on the cost-effectiveness plane (Figure 2.5). If the incremental costs and effects are plotted to the right (below) of this line on the CE plane, then the treatment is considered cost-effective, while points to the left (above) of this line represent cost-ineffective interventions (Briggs and Tambour 2001).

Due to uncertainty often surrounding estimates of cost-effectiveness or cost-utility, additional analysis is required. Non-parametric bootstrapping is one of

the methods that has been widely adopted and used in both cost-effectiveness and cost-utility studies for deriving confidence intervals for the ICER (Briggs et al. 1997). Non-parametric bootstrapping is a re-sampling method, which involves simple random sampling with replacement from the original data to build an empirical estimate of the sampling distribution of the ICER (Briggs et al. 1997, Drummond et al. 2015). This resampling is repeated a large number of times (for example, 1,000 to 5,000 times). Figure 2.6 provides an example of a cost-effectiveness plane with bootstrapped incremental cost and QALY dyads and two cost-effectiveness thresholds (the diagonal lines) of £20,00 and £30,000 per QALY.

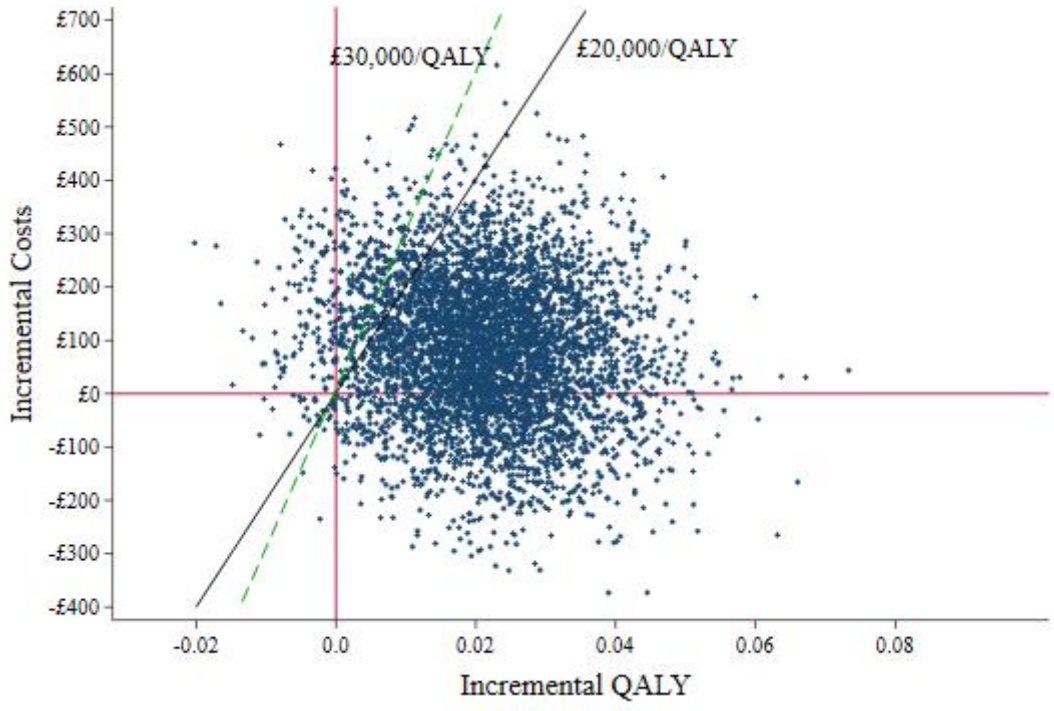

Figure 2.6 Cost-effectiveness plane comparing the intervention group to the control group
Doted green line represents £20,000/QALY willingness to pay threshold; dark blue line is £30,000/QALY threshold. Reproduced from (Li et al. 2018).

Besides estimating CIs for the ICER, non-parametric bootstrapping can construct a cost effectiveness plane with the bootstrapped replicates, while the corresponding cost-effectiveness acceptability curve (CEAC) can then be constructed based on the uncertainty in costs and effects differences. This CEAC shows the probability that an intervention is cost effective given the observed data, compared to its comparator at a range of willingness to pay thresholds / cost-effectiveness thresholds. Figure 2.7 is an example of a CEAC for an

intervention with 87% probability of being cost effective at the £20,000 per QALY threshold, and 92% probability of being cost effective at the £30,000 per QALY threshold (reproduced from (Li et al. 2018)).

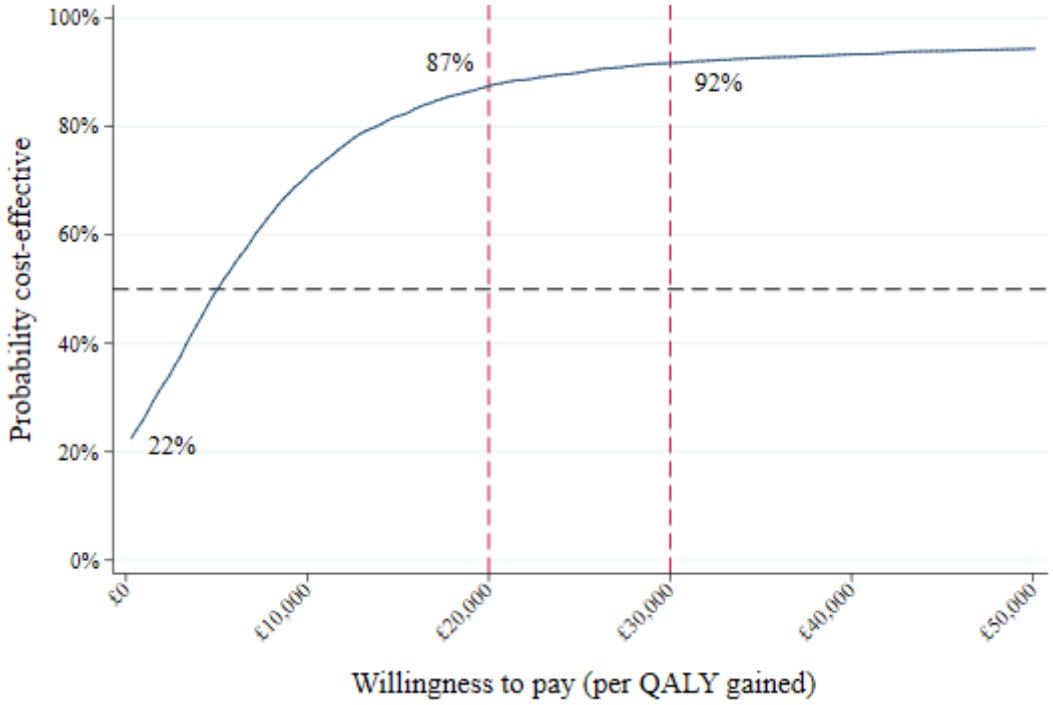

Figure 2.7 Cost-effectiveness acceptability curve

Reproduced from (Li et al. 2018).

2.8.2 Economic evaluation checklists

Healthcare EEs pose a particular challenge for reporting because substantial information must be conveyed to allow scrutiny of study findings (Husereau et al. 2013a). EE checklists are a common method to standardize assessments of quality when reviewing the quality of submitted and published EEs (Drummond and Jefferson 1996, Watts and Li 2019). They also can provide a framework for researchers planning and conducting EEs, as to be useful, EE studies should be methodologically comparable, of high quality and relevant for the health care decision context (Langer 2012).

Many EE checklists have been published to date. A recent meta-review of systematic reviews of health economic evaluations, which aimed to describe how checklists have been used in these systematic reviews (Watts and Li 2019), found that the use of checklists varied substantially. Watts and colleagues identified

346 reviews published between 2010 and 2018 that used checklists. The most common checklist used was the 36-item Drummond and Jefferson checklist from the British Medical Journal (Drummond and Jefferson 1996), which was used in 117 (30%) reviews in total. The second most common checklist was the Consensus on Health Economic Criteria (CHEC)-list used in 77 (18%) reviews (Evers et al. 2005). After these were the Philips checklist (n = 59 [13%]) (Philips et al. 2006), the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (n = 59 [13%]) (Husereau et al. 2013a, Husereau et al. 2013b), the Quality of Health Economic Studies (QHES) checklist (n = 58 [13%]) (Chiou et al. 2003) and the Drummond 10-item checklist (n = 41 [9%]) (Drummond et al. 2005a). However, the CHEERS checklist has experienced the largest increase in use since its development and was the most frequently used instrument in the most recent years: as of 2017, the CHEERS checklist is the most commonly used checklist, followed by the CHEC list and the Drummond and Jefferson checklist.

The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (Husereau et al. 2013a, Husereau et al. 2013b) was developed specifically to optimise the reporting of health economic evaluations. It was developed by a task force supported by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR), as part of a broader initiative to facilitate and encourage the interchange of expert knowledge and develop best practices (Husereau et al. 2013b). The CHEERS task force members were chosen by the chair of the task force primarily based on their longstanding academic expertise and contribution to the multidisciplinary field of health economic evaluation. The task force consisted of editors of health economic journals and content experts from around the world. The resulting guidance was co-published in ten health economics and medical journals to ensure wide dissemination.

The CHEERS checklist contains 24 items, which are subdivided into six main categories: (1) Title and abstract; (2) Introduction (background and objectives); (3) Methods (target population and subgroups; setting and location; study perspective; comparators; time horizon; discount rate; choice of health outcomes; measurement of effectiveness; measurement and valuation of preference based outcomes; estimating resources and costs; currency, price

date, and conversion; choice of model; assumptions; analytical methods); (4) Results (study parameters; incremental costs and outcomes; characterising uncertainty; characterising heterogeneity); (5) Discussion (study findings, limitations, generalisability, and current knowledge); and (6) Other (source of funding; conflicts of interest). The full CHEERS checklist can be found in Appendix 4.

2.9 Vehicles for economic evaluation

Evidence about cost-effectiveness can be obtained through various vehicles, including randomised controlled trials and decision analytical modelling (such as decision trees, Markov models, and other modelling approaches). These two types of vehicles for economic evaluation (EE) are covered in brief in this section.

2.9.1 Economic evaluations alongside clinical trials

Randomised controlled trials (RCTs) are commonly used as a vehicle for conducting economic evaluations of healthcare interventions and programmes. Many funders, such as the UK National Institute for Health Research Health Technology Assessment Programme And the UK Medical Research Council, routinely request that assessments of cost effectiveness are incorporated in the design of RCTs (Petrou and Gray 2011, Glick et al. 2014). When an RCT is being used as a vehicle for EE, the trial provides the sole source of evidence on resource use and health effects that forms the basis of the estimate of cost-effectiveness (Briggs et al. 2006). Collecting economic data at the same time as evidence of effectiveness maximises the information available for analysis but requires proper consideration at the trial design stage (Petrou and Gray 2011).

EEs conducted alongside RCTs have several advantages. They provide an early opportunity to produce reliable estimates of cost-effectiveness at low marginal cost. EEs conducted alongside RCTs allow for unbiased estimates of treatment effects, as well as allow collection of outcome and resource use information prospectively and obtain patient-specific data. Access to individual patient data also permits a wide range of statistical and econometric techniques (Petrou and Gray 2011). However, it has been also recognised that trials may exhibit certain

weaknesses. This includes the limited number of comparisons, short follow-up (for example, not allowing estimation of cost-effectiveness over a lifetime), limited comparators, restricted generalisability to different settings or countries, and the failure to collect all the evidence needed to address cost-effectiveness (Briggs et al. 2006, Petrou and Gray 2011). A large proportion of economic evaluation studies could be described as trial-based EEs. Since the 1990s approximately 30% of published economic valuations on the NHS Economic Evaluation Database have been based on data from a single trial (Briggs et al. 2006). Notwithstanding the earlier mentioned limitations of trial-based evaluations, they are likely to continue to have an important role in producing reliable estimates of cost effectiveness (Petrou and Gray 2011).

According to Glick an colleagues (Glick et al. 2014), six sets of issues are needed to be considered at the design stage of an RCT. These include: 1) What pre-planning should be done in preparation for the trial? 2) What resource use should be measured? 3) In what form should the data be collected? 4) Which unit cost estimates should be used for the study? 5) How naturalistic should the study design be? and 6) What should be done if the full benefit and cost of an intervention are not expected to be observed during the period of observation in the trial?

A case study of an EE alongside an RCT is presented in two chapters of this thesis: Chapter 5 presents the methods and Chapter 6 the results of this EE.

Cost-effectiveness observed within a trial may be substantially different from what would have been observed with continued patient follow-up and, as a consequence, extrapolation of cost-effectiveness over an extended period, often a lifetime, is considered important (Petrou and Gray 2011). One of the means of such extrapolation is decision analytical modelling, described below.

2.9.2 Decision analytical modelling

In economic valuation, a decision analytic model uses mathematical relationships to define a series of possible consequences that would flow from a set of alternative options being evaluated (Briggs et al. 2006). A decision model

can be based entirely on previously published evidence, or it can be built using purposefully collected data from a trial. This could be supported by a wider range of data beyond the trial time frame on costs and effects from other sources, such as observational studies and meta-analysis, to be synthesised within the model in order to derive cost-effectiveness outcomes (Edwards and McIntosh 2019). Based on the inputs into the model, the likelihood of each consequence is expressed in terms of probabilities, and each consequence has a cost and an outcome. This way it is possible to calculate the expected cost and expected outcome of each option under evaluation. For a given option the expected cost (or outcome) is the sum of the costs (or outcomes) of each consequence weighed by the probability of that consequence. A key purpose of decision modelling is to allow for the variability and uncertainty associated with all decisions (Briggs et al. 2006). In recent decades there has been an increased interest in decision analytic modelling as a vehicle for economic valuation in healthcare (Briggs et al. 2006).

2.10 Economic evaluation of public health interventions

As the Protecting Teeth @ 3 trial, which forms the basis of this thesis, is a child public health intervention (PHI), as is the integrated Childsmile programme overall, this section is dedicated to specifics of EEs of PHIs.

Increasing attention has been given to the evaluation of PHIs over the last decade (Weatherly et al. 2009). An emerging applied subdiscipline of health economics is referred to as “public health economics”, which may be defined as how society uses scarce resources to meet preventive healthcare needs, prevent ill health, reduce inequality in health, and more widely promote human thriving through the life course (Edwards et al. 2016). Economic evidence can provide insight into the value of public health investments to the overall health system. Evidence suggests that increased investment in preventive activities and improvements in public health practise and decision-making produce measurable and sustainable health gains (Rabarison et al. 2015).

2.10.1 Challenges specific to economic evaluations of public health interventions

PHIs are delivered out-with the health care setting often in schools and communities, can generate broad costs and benefits and are often directed at populations or communities rather than specific individuals. This results in a series of challenges specific to economic evaluations of PHIs (Weatherly et al. 2009). Weatherly and colleagues investigated five reviews that had explored the economics of public health, with an aim to identify the methodological challenges present. The authors identified four methodological challenges for assessing cost-effectiveness of PHIs: attribution of effects, measuring and valuing outcomes, identifying intersectoral costs and consequences, and incorporating equity considerations. The first challenge is *attribution of effects*. In current economic evaluation practice, there is a preference for evidence derived from randomised controlled trials (RCTs) comparing the relevant alternatives. As it is relatively difficult to undertake RCTs on PHIs, there is likely to be fewer RCTs in this area. Therefore, other approaches for obtaining unbiased estimates of intervention effects might be necessary. In addition, measured outcomes are usually short-term while public health programmes, especially prevention programmes, may impact on health over the longer term. The second challenge is *measuring and valuing outcomes*. Health outcomes are typically measured in QALYs, estimation of which requires both projections of long-term outcomes and the classification and valuation of health outcomes. Other outcomes might also have to be considered in evaluations of PHIs, for example, the effects that interventions might have on individuals not directly targeted by the programme and/or non-health-related outcomes. The next methodological challenge is *identifying intersectoral costs and consequences*. Due to the fact that the impacts of PHIs are wide-ranging, costs and benefits associated with such an intervention might fall on many parts of the public sector. The broad nature of the costs and benefits in PHIs requires an intersectoral approach to identify them. The final challenge outlined by the authors is *incorporating equity considerations*. Many PHIs are concerned with health inequalities, whereas standard economic evaluation methods focus on efficiency (the maximization of health gain) rather than on equity (the distribution of health gains). Consequently, the evaluation of PHIs may need to

pay more attention to equity considerations. The normal assumption in economic evaluation studies is that the value of a QALY is the same, no matter who receives it. However, as tackling inequalities is one of the primary goals of PHIs, the distribution of QALY gains between population sub-groups has a particular importance (Weatherly et al. 2009).

In addition to the four main challenges identified, Weatherly and colleagues also mentioned two additional issues: *discounting future costs and benefits* and *the characterisation of uncertainty*. The choice of discount rate is particularly important when evaluating health programmes, which generate benefits far into the future (most public health programmes, but also clinical preventative measures). In the UK, NICE recommends using a lower discount rate for PHIs as they act over a long term: a discount rate of 1.5% is used for all costs and benefits in base-case analysis, while in sensitivity analysis a discount rate of 3.5% on both costs and benefits is used (NICE 2012). With regards to characterisation of uncertainty (there is considerable uncertainty regarding some of the future benefits of PHIs), some experts argue that a probabilistic sensitivity analysis is required in all cases, while others believe that simpler methods will suffice (Weatherly et al. 2009).

In 2003 the Chancellor of the Exchequer asked Sir Derek Wanless to undertake a review of cost-effective approaches to improving public health, prevention and reducing health inequalities. One of the findings of the Wanless Report - Securing Good Health for the Whole Population - published in 2004 was the lack of evidence about the cost-effectiveness of PHIs and preventive policies (Wanless 2004). The report stated that the body of economic evidence relating to PHIs was small in comparison to that related to health care. Since then NICE have included a section on incorporating health economics to their methods for the development of NICE public health guidance (NICE 2012).

2.10.1.1 NICE's public health guidance: Incorporating health economics

In this section relevant information from Section 6 – Incorporating health economics of Methods for the Development of NICE Public Health Guidance (NICE 2012) is briefly presented.

In 2012 NICE broadened its approach to the appraisal of PHIs and placed more emphasis on cost–consequences analysis (CCA) and cost–benefit analysis (CBA), because QALY, as an outcome measure used in cost–utility analysis (CUA), may fail to capture the full range of benefits across different sectors resulting from a PHI. CCA can measure both welfare and quality of life more broadly than CUA. It can take many other items into account that decision-makers in local authorities may find important. CBA, on the other hand, allows all societal costs and all benefits to be included, and expressing both costs and benefits in money terms avoids the difficulties of aggregating data that occur in CCA. However, cost-effectiveness analysis (CEA) and CUA are still required routinely, due to several reasons: a) CUA provides a single "yardstick" or "currency" for measuring the impact of interventions on health; b) CUA allows interventions in healthcare to be compared so that resources may be allocated more efficiently; c) In some circumstances, almost all benefits are health benefits. In that case, further analysis (such as CCA or CBA) would not be required.

The NICE public health reference case (NICE 2012) proposed to use a public sector perspective, instead of the NHS and personal social services perspective recommended in the reference case for the evaluation of new drugs and clinical health programmes (NICE 2013b). In addition to the public sector perspective, the perspective of the department that administers the PHI should be used (for example, local government or an NHS perspective). As was mentioned earlier, for PHI evaluations NICE recommends using a lower discount rate of 1.5 for all costs and benefits in base-case analysis, and a higher discount rate of 3.5% in sensitivity analysis. A summary of the NICE's public health reference case is provided in Table 2.5.

Table 2.5 Summary of NICE's public health reference case

Element of assessment	Reference case
Defining the decision problem	The scope developed by NICE
Comparator	Interventions routinely used in the public sector, including those regarded as best practice
Perspective on costs	Public sector, including the NHS and personal social services (PSS), or local government Societal perspective (where appropriate)
Perspective on outcomes	All health effects on individuals. For local government guidance, non-health benefits may also be included
Type of economic evaluation	CCA CBA CUA – to ensure comparability with other parts of NICE
Synthesis of evidence on outcomes	Based on a systematic review
Measure of health effects	QALYs
Measure of non-health benefits	Where appropriate, to be decided on a case-by-case basis in conjunction with the Centre for Public Health Excellence (CPHE) technical team
Source of data for measurement of health-related quality of life (HRQL)	Reported directly by patients or carers
Source of preference data for valuation of changes in HRQL	Representative sample of the public
Discount rate	An annual rate of 1.5% on both costs and health effects (sensitivity analyses should include discount rates used by other parts of NICE, 3.5%)
Equity weighting	An additional QALY has the same weight, regardless of the characteristics of the individuals who gain the health benefit

Source: Table 6.1 in Methods for the Development of NICE Public Health Guidance (NICE 2012).

For many PHIs, it will be necessary to extrapolate effectiveness evidence over long time periods. It will also be necessary to derive long-term quality-adjusted life year (QALY) outcomes from short-term, intermediate results. Various modelling techniques can be used for this.

2.10.2 The cost-effectiveness of public health interventions

A review of cost-effectiveness estimates using English cost data that were collected and analysed from 21 economic analyses underpinning public health guidance published by NICE between 2006 and 2010 (Owen et al. 2012), concluded that the majority of the assessed PHIs were highly cost-effective. The authors analysed 200 base-case cost-effectiveness estimates. Out of these, 15%

were cost saving (the intervention was more effective and cheaper than comparator), 85% were cost-effective at a threshold of £20,000 per QALY and 89% at the higher threshold of £30,000/QALY. Only 5.5% were above £30,000, and further 5.5% of the interventions were dominated (the intervention was more costly and less effective than the comparator). Owen and colleges highlighted that only 4% of the NHS budget (Marmot Review 2010) was spent on prevention and that there was a paucity of evidence on the cost-effectiveness of PHIs. Their analysis showed that the PHIs considered by NICE were generally highly cost-effective according to the NICE threshold and that they represented good value for money.

A more recent review looked at return on investment of PHIs (Masters et al. 2017). Masters and colleagues' systematic review had been partly prompted by government cuts to public health budgets in England, and the authors focused on PHIs delivered in other high-income countries in order to maximise UK relevance. Studies that calculated a return on investment (ROI) or cost-benefit ratio (CBR) for PHIs in high-income countries were identified and 52 studies were included into the review. ROI and CBR are two forms of economic evaluation that value the financial return (benefits) of an intervention against the total costs of its delivery. The CBR is the benefit divided by the cost, and the ROI is the benefit minus the cost expressed as a proportion of the cost, that is, the CBR−1. The median ROI for PHIs was 14.3 to 1, and median CBR was 8.3. The median ROI for all 29 local PHIs was 4.1 to 1, and median CBR was 10.3. Even larger benefits were reported in 28 studies analysing nationwide PHIs; the median ROI was 27.2, and median CBR was 17.5. PHIs at a local level had a median a ROI of 4, meaning that every pound invested yields a return of £4 plus the original investment back. "Upstream" interventions delivered on a national scale generally achieved even greater returns on investment: the median ROI for national programmes was 27, whereas legislation had the median ROI of 46. The results of the systematic review suggested that local PHIs were cost-saving, and offered substantial returns on investment, nationwide programmes even more so, therefore, as the authors concluded, the cuts to public health budgets represented a false economy.

However, the results and the conclusion of Macmaster and colleagues' review have to be interpreted with caution. Their systematic review sparkled a further debate. For example, in a Public Health England (PHE) official blog, Brian Ferguson, Chief Economist for PHE, posted regarding what is usually meant when a question "are public health interventions 'cost-saving'?" is asked (Ferguson 2018). He argued that often it means whether the intervention delivers cashable financial savings to government budgets within the next two to five years. He emphasised that it was not possible to conclude from the review that PHIs were "cost-saving" in the narrow sense of delivering short-term cashable savings (some interventions might be cost-saving in this way, but it could not be implied from the evidence presented in the Macmaster and colleagues review). Given the obvious interest in short-term savings among local government and NHS decision-makers, a useful recommendation might be that future CBA and ROI studies provide narrower, short-term, budget-focused breakdowns, as well as findings from a broader longer-term societal perspective. On the other hand, it is equally important to recognise the ethical point that the aim of public policy is not solely to achieve maximum savings to public sector budgets, but also to improve people's health and wellbeing and reduce health inequalities (Ferguson 2018). David Buck at the King's Fund, an independent charitable organisation working to improve health and care in England, warns that it is unknown how that £14 return (the median ROI for PHIs in Macmaster and colleagues' review), breaks down into cash saving or health or other outcomes of value since the authors didn't report this information (Buck 2018). He also urged that there should be more standardisation of inclusion and reporting criteria for ROI studies in public health.

2.11 Summary

This chapter provides a detailed overview of economics and health economics concepts and introduces economic evaluation terms and methodological approaches specific to public health economic evaluation relevant to this thesis. The concept of market failure was introduced, and it was explained how economic evaluation helps to reconstruct the missing market in healthcare. Economic evaluation frameworks (CEA, CUA, CBA, CCA and CMA) were described and critiqued, as well as the concepts of quality-adjusted life year and health-

related quality of life. Overviews of adult and child/adolescent preference-based health-related quality of life measures and of direct preference elicitation methods were provided. Issues related to costing and economic evaluation perspectives, technical issues in economic evaluation, existing guidelines for reporting and presentation of economic evaluation results, and vehicles for economic evaluation were also covered. Specific attention was given to economic evaluations of PHIs, including existing challenges, NICE's health economics public health guidance and an overview of cost-effectiveness of PHIs.

This chapter sets the scene for the following chapters, which focus on economic evaluations of primary caries prevention in preschool children (Chapter 3), on instruments for measuring health-related quality of life in preschool children (Chapter 4), and on the economic evaluation of the Protecting Teeth @ 3 randomised controlled trial, based on the nursery fluoride varnish segment of the Childsmile programme (Chapters 5 and 6).

Chapter 3 Systematic review of economic evaluations of primary caries prevention in two- to five-year-old preschool children

3.1 Introduction to Chapter 3

The high prevalence of caries around the world, combined with the high costs associated with the disease, pose an important preventive healthcare problem. Economic evaluation (EE) can be adopted to examine the cost-effectiveness of caries prevention programmes (Morgan et al. 2012). This can aid decision-makers in making rational judgments to efficiently utilize limited resources (Tonmukayakul et al. 2015) and to help plan future initiatives. As it was shown in Section 2.10, public health interventions can be highly cost-effective, and EEs have been used to evidence the cost-effectiveness of preventive caries programmes (Anopa et al. 2015).

A number of child public health caries prevention strategies and intervention types currently exist, and choosing between competing oral public health programmes is not always an easy decision for public health planners (Morgan et al. 2012). In a recent critique, Watt et al. recommended that the priority for oral health (OH) research should be the promotion of applied health service and implementation research, with methodologies including EE, so that planners are able to assess programme performance comprehensively (Watt et al. 2019). EEs help decision-makers to allocate limited resources the best way, in order to achieve the greatest health benefit. A full EE is *"a comparison of two or more alternative courses of action, while considering both inputs (costs) and outputs (consequences) associated with* each" (Drummond et al. 2015). As was discussed earlier in Chapter 2, Section 2.5, the most common types of full EEs are cost-benefit analysis (CBA), cost-effectiveness analysis (CEA) and cost-utility analysis (CUA). A partial EE measures a programme/intervention or disease costs, but does not involve a comparison with alternative options and/or does not relate costs to outcomes (Rabarison et al. 2015). Partial EEs include programme/intervention cost analysis, cost-outcome description and cost-of-illness analysis.

In recent years, the number of published cost-effectiveness studies on the prevention of dental diseases has increased (Marino et al. 2013, Tonmukayakul et al. 2015), however, a recent systematic map of systematic reviews in paediatric dentistry (Mejare et al. 2015) revealed that the cost-effectiveness of the majority of strategies for the management of dental conditions in children and adolescents remained uncertain. A systematic review of EE publications in dentistry (Tonmukayakul et al. 2015), which covered all age groups, revealed that over half of the total 114 studies included were EEs of dental caries prevention. The review identified some common methodological limitations, such as absence of sensitivity analysis, discounting, and insufficient information on how costs and outcomes had been measured and valued. The authors concluded that EE studies in dentistry had increased over the last forty years in both quantity and quality. However, a number of publications failed to satisfy some components of standard EE research methods.

According to a review of publications on EEs of caries prevention programmes in all ages (Marino et al. 2013) the main methodological problems identified were the limited information provided on adjustments for discounting in addition to inadequate sensitivity analyses, similar to the conclusions of Tonmukayakul and colleagues (2015). In addition, a more recent systematic review of EEs in child OH research, which included full EE studies involving children aged 18 years old and under (Rogers et al. 2019), highlighted that a wide range of outcome measures was employed across the reviewed studies, which prevented inter-study comparisons. Lack of meaningful involvement of children and of consideration of their own perspectives and preferences were also emphasised.

Experiences and health-related behaviour patterns in early life are known to affect OH throughout the life-course. Consequently, calls have been made for priority to be given to interventions targeting early ages (ICOHIRP 2015). Economic evidence suggests that there may be significant returns to early investment specifically with regards to caries prevention (Anopa et al. 2015, Public Health England 2016c, York Health Economics Consortium 2016e). Therefore, this age group is the focus of the present systematic review. Just a few studies conducted in preschool populations were identified in recent reviews of EEs of OH interventions (Coffin et al. 2013, Hettiarachchi et al. 2018). There

is only one non-systematic review, which collated the evidence on the cost-effectiveness of interventions to improve the OH of younger children, aged 0-5 years (York Health Economics Consortium 2016e). This rapid review with a narrow search timeframe (between 2012 and 2016) found only five studies meeting the inclusion criteria. The authors found scarce cost-effectiveness evidence but warned that this should not be interpreted as evidence that those interventions were not effective or cost-effective.

This chapter therefore represents the first systematic review of EEs of primary caries prevention, which is focused specifically on preschool children aged two to five years. Primary caries describes a lesion on a previously sound surface, as opposed to secondary or recurrent caries - a lesion which develops adjacent to a restoration (Machiulskiene et al. 2020). This review includes both full and partial EEs and uses a formal quality assessment tool. The Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist, the most recently developed EE checklist that was created to update previous guidelines (Husereau et al. 2013b, Frederix 2019), was used to assess the reporting quality of the included full EE studies.

3.2 Aim and objectives

The overall aim of this chapter was to conduct a systematic review of scientific papers on EEs of primary caries prevention in preschool children aged two to five years and to further evaluate the reporting quality of the included full EE studies.

Objectives: a) To describe and summarise currently available scientific literature on EEs of primary caries prevention in preschool children aged two to five years; b) To evaluate the reporting quality of the included full EE studies, using a quality assessment tool developed for appraisal of economic evaluations.

3.3 Systematic review methods

The review followed the Preferred Reporting System for Systematic Reviews and Meta-Analysis (PRISMA) strategy (Liberati et al. 2009). The protocol of this

systematic review was registered in the international database of prospectively registered systematic reviews in health and social care (PROSPERO), Centre for Reviews and Dissemination, University of York (No: CRD42017083732) (Anopa et al. 2017).

3.3.1 Eligibility criteria

A structured approach for framing questions that uses five components – Participants, Interventions, Comparators, Outcomes, and Study design (PICOS) (Schardt et al. 2007, Liberati et al. 2009) – was used in developing the eligibility criteria. The interventions of interest were oral health interventions aimed at primary caries prevention in children aged 2-5 years (e.g. water fluoridation, fluoride toothpaste, fluoride varnish / gel, fluoride tablets, fissure sealant, oral health educational interventions, etc.). Studies on interventions aimed at secondary caries prevention were not included (e.g. restorative treatment of existing caries). To be included into this review a study had to report relevant results for children aged between two and five years old (inclusive). At least some age groups from this range had to be reported. All types of economic evaluations were included: full economic evaluations (e.g. employing CEA, CBA or CUA) and partial economic evaluations (e.g. cost analysis, cost-outcome description). A full list of inclusion and exclusion criteria is presented in Table 3.1.

Table 3.1 Eligibility criteria

Parameter	Inclusion	Exclusion
Population	Children aged between 2 and 5 years old (inclusive). At least some age groups from this range have to be reported.	– Participants younger or older than 2-5 years. – Studies with participants aged around 5 years at baseline who were then followed up into older ages – Studies of mixed populations where data are not reported for eligible children separately.
Interventions	Oral health interventions aimed at primary caries prevention in preschoolers (e.g. water fluoridation, fluoride toothpaste, fluoride varnish application, fluoride gels/tablets, fissure sealant, oral health educational interventions, etc.).	– Oral health interventions other than those specified by the inclusion criteria (e.g. restorative treatment of existing caries). – Studies of interventions where the data for oral interventions aimed at caries prevention are not reported separately.
Comparators	– Other oral health interventions – No intervention – No comparator (e.g. a cost analysis of a single intervention)	Studies of interventions where the data for oral interventions aimed at caries prevention are not reported separately.
Outcomes	The study must include both: – Cost-effectiveness outcomes (e.g. cost per quality-adjusted life year (QALY), cost per filling avoided, cost per extraction avoided) or other economic outcomes (e.g. results of a cost analysis, intervention costs, return on investment of the initiative); and – Oral health outcomes (e.g. levels of tooth decay, numbers of fillings, numbers of teeth removed, quality of life) or other outcomes reflecting the oral health state (e.g. number of dental visits or dental treatments)	– Non-oral health outcomes. – Non-economic outcomes.
Study designs	– Full economic evaluations (e.g. employing cost-effectiveness, cost-utility, cost-benefit, cost-minimisation or cost-consequence analyses) – Partial economic evaluations (e.g. cost analysis, cost-outcome description, cost of illness)	Studies with no economic evaluation component
Publication type	Original study papers with available full text, published in a peer-reviewed journal	– Systematic and other reviews – Abstracts – Conference proceedings – Letters to editor – Case reports – PhD / Doctoral Theses – Study protocols
Language	Any language	
Publication date	Up to 19/12/2017 (when the searches were run)	

3.3.2 Data sources and search strategy

A systematic literature search was conducted in the following health sciences and psychological electronic databases: MEDLINE and EMBASE (via the Ovid platform), and EconLit (via the EBSCO platform). Several previous systematic reviews of economic evaluations of oral health interventions, their search strategies used and reference lists were consulted (Kallestal et al. 2003, Coffin et al. 2013, Marino et al. 2013, Tonmukayakul et al. 2015, York Health Economics Consortium 2016e, Hettiarachchi et al. 2018). Reference lists of the studies included in this systematic review were screened for any additional eligible studies.

Search strategies and search terms for this systematic review were developed based on the standardised EE filters (Glanville et al. 2009, CADTH 2016) with the help from a University of Glasgow subject librarian, Mr Paul Cannon (Cannon 2017), in autumn 2017. Further, the University of York's Centre for Reviews and Dissemination (CRD) guidance for undertaking systematic reviews in health care (Centre for Reviews and Dissemination 2008) was used, in particular Chapter 5, Systematic Reviews of EEs, in the process of developing and conducting this review. In addition, a series of papers on how to conduct a systematic review of EEs were consulted (Thielen et al. 2016, van Mastrigt et al. 2016, Wijnen et al. 2016).

No publication time or language restrictions were applied. It was planned that should any relevant papers be identified in languages other than English or Russian, these would be to be translated with a help of professional translation services.

The following blocks of search terms were used: a) The Canadian Agency for Drugs and Technologies in Health (CADTH) based search filter (including various types of EEs, economics, costs and economic modelling); b) Oral health (OH), caries and OH interventions terms. OH experts were consulted to select the typical terms (such as: oral health, caries, early childhood caries, dental decay; toothbrushing, toothpaste, fluoride, fissure sealant, chlorhexidine, mouthwash; educational, preventive and promotional oral health initiatives, etc.); and c)

Terms related to preschool age (e.g. toddler, infant, preschool, early childhood, nursery, kindergarten, early years). A separate block of search terms was related to literature reviews. At the last stage of the search, such reviews were removed from the results of the search. An example of the search strategy conducted in Medline is shown in Appendix 3.

3.3.3 Study Selection Procedure

Titles and abstracts of all retrieved records were screened against the inclusion criteria by one reviewer (Yulia Anopa, YA), using a method developed by Bramer and colleagues (Bramer et al. 2017) employing EndNote (Clarivate Analytics, Philadelphia, USA). Citations with a title but no abstract were assessed for relevance based on the title only, and if the reviewer felt that a paper might be relevant, an effort was made to acquire the full text. Twenty percent of all titles and abstracts were checked by a second reviewer, one of the PhD supervisors (Emma McIntosh, EM, or Lorna Macpherson, LM). Any disagreements were resolved by consensus-seeking discussions between all three reviewers. The full texts of all potentially relevant articles were retrieved and screened by one reviewer (YA) with any questionable cases discussed with a second reviewer (EM or LM) or between all three reviewers, depending on the nature of an issue.

3.3.4 Data extraction

Descriptive study data were extracted using a pre-tested data extraction template. Several sources were used during the development of an initial draft data extraction template: CRD's guidance for undertaking systematic reviews in health care (Centre for Reviews and Dissemination 2008), data extraction templates used in two previous reviews (York Health Economics Consortium 2016e, Hettiarachchi et al. 2018) and the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (Husereau et al. 2013b). The draft template was tested on four papers that employed different types of economic analysis (e.g. CEA or cost analysis), were of different study type/design (e.g. a Markov model or observational study or evaluation alongside a randomised controlled trial, RCT) and were published within a wide time range. The proposed draft template was then discussed at a meeting between all

three reviewers and the data extraction template was finalised. Data extraction fields included into the final data extraction template are shown in Box 3.1. Data were extracted by one reviewer (YA) and a randomly selected 20% were checked by a second reviewer (EM). Any disagreements were resolved by a discussion within the full review team.

Box 3.1 Data extraction fields

Study main author
Year of publication
Country
Aim of study
Type of study / Study design
Type of economic evaluation (full or partial)
Further type of economic evaluation (e.g. CUA, CBA, CEA, CMA; cost analysis, return on investment, cost-outcome description, cost of illness, etc.)
Participant characteristics:
- Mean or median age (with range) at baseline/or other point; Proportion of 2-5 y.o., if a wider age group was participating
- Number of participants (separately for 2-5 y.o., if stated)
- Participant description
Setting (e.g. nursery; school; community dental clinic; general dental practice; hospital; modelling based on multiple sources; other details)
Study perspective
Intervention(s) (description)
Comparator(s) (description)
Outcomes:
- Oral health outcomes (type)
- Cost-effectiveness / other economic outcomes (type):
* Preference based
* Non-preference based
- Other economic "outcomes" (type) (If not cost-effectiveness, e.g. costs only)
Time horizon / Duration of study
Discount rate
Summary of model / methods used (in particular, economics related)
Currency
Base year
Sensitivity analysis (Yes/No and type)
Results (short outline, economics related in particular, including sensitivity analysis)
Authors' conclusions

3.3.5 Reporting quality assessment of full economic evaluations

The reporting quality of full economic evaluations, which formed a subset of the overall pool of papers included into this systematic review, was assessed with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (Husereau et al. 2013a, Husereau et al. 2013b). The CHEERS checklist was developed by a task force supported by the International Society for Pharmacoeconomics and Outcomes Research (ISPOR) specifically to optimise the reporting of health economic evaluations. It attempted to consolidate and update previous health economic evaluation guidelines efforts into one current, useful reporting guidance (Husereau et al. 2013b). In recent years the CHEERS checklist has been widely used in systematic reviews of economic evaluations in healthcare (as of 2017, the CHEERS checklist was the most commonly used checklist out of all existing EE checklists) (Watts and Li 2019) including those of oral health interventions (Hettiarachchi et al. 2018, Rogers et al. 2019, Amilani et al. 2020).

The CHEERS checklist contains 24 items, which are subdivided into six main categories: (1) Title and abstract; (2) Introduction (background and objectives); (3) Methods (target population and subgroups; setting and location; study perspective; comparators; time horizon; discount rate; choice of health outcomes; measurement of effectiveness; measurement and valuation of preference based outcomes; estimating resources and costs; currency, price date, and conversion; choice of model; assumptions; analytical methods); (4) Results (study parameters; incremental costs and outcomes; characterising uncertainty; characterising heterogeneity); (5) Discussion (study findings, limitations, generalisability, and current knowledge); and (6) Other (source of funding; conflicts of interest). The full checklist is shown in Appendix 4.

Each item of the CHEERS checklist was scored as "1" / "Yes", if the paper meets the criteria in full; "0" / "No", if it does not met the criteria; or "Not applicable". Partial scores were not assigned. The items from “Other” category, namely “Source of funding” and “Conflicts of interest” were not taken into account when calculating a total score for each paper, as these are not directly relevant to the economics related reporting quality of a paper, and as one or both of

these items were often not met. Thus, a total of 22 was the maximum possible score. Each study's reporting quality was expressed as a proportion of items fully met for each paper (out of 22 in total, for papers with all checklist items applicable to their contents; or out of the total number of applicable items for the papers where not all items were applicable). One reviewer (YA) assessed all of the selected papers using the CHEERS checklist with a second reviewer (EM) assessing 20% of these papers, selected at random. Any discrepancies were resolved by discussion between the two reviewers.

3.4 Results

3.4.1 Literature databases search results

808 studies were identified, of which 42 (5%) met the inclusion criteria. At the title and abstract screening phase the agreement rates between the author and each of the two second reviewers were 90% and 98%, respectively (each of the second reviewers were assigned a random 20% of the total number of identified studies, i.e. 80 titles/abstracts each). Cases of titles and abstracts, which were disagreed upon by the two reviewers, were discussed on an individual basis among all three reviewers and, based on consensus, were voted in or out.

Figure 3.1, a PRISMA flow diagram, illustrates the study selection process. A set of three papers reported on the same study (Ast et al. 1965, Ast et al. 1967, Ast et al. 1970), with two of them reporting on intermediate results. Only the latest of the three, reporting the study in full, was included into further review (Ast et al. 1970). Two papers reported on another study, one of them being a Health Technology Assessment (HTA) report (Tickle et al. 2016) and another a conventional journal paper (O'Neill et al. 2017). The latter was included into the review. The final number of papers included into the review was 39.

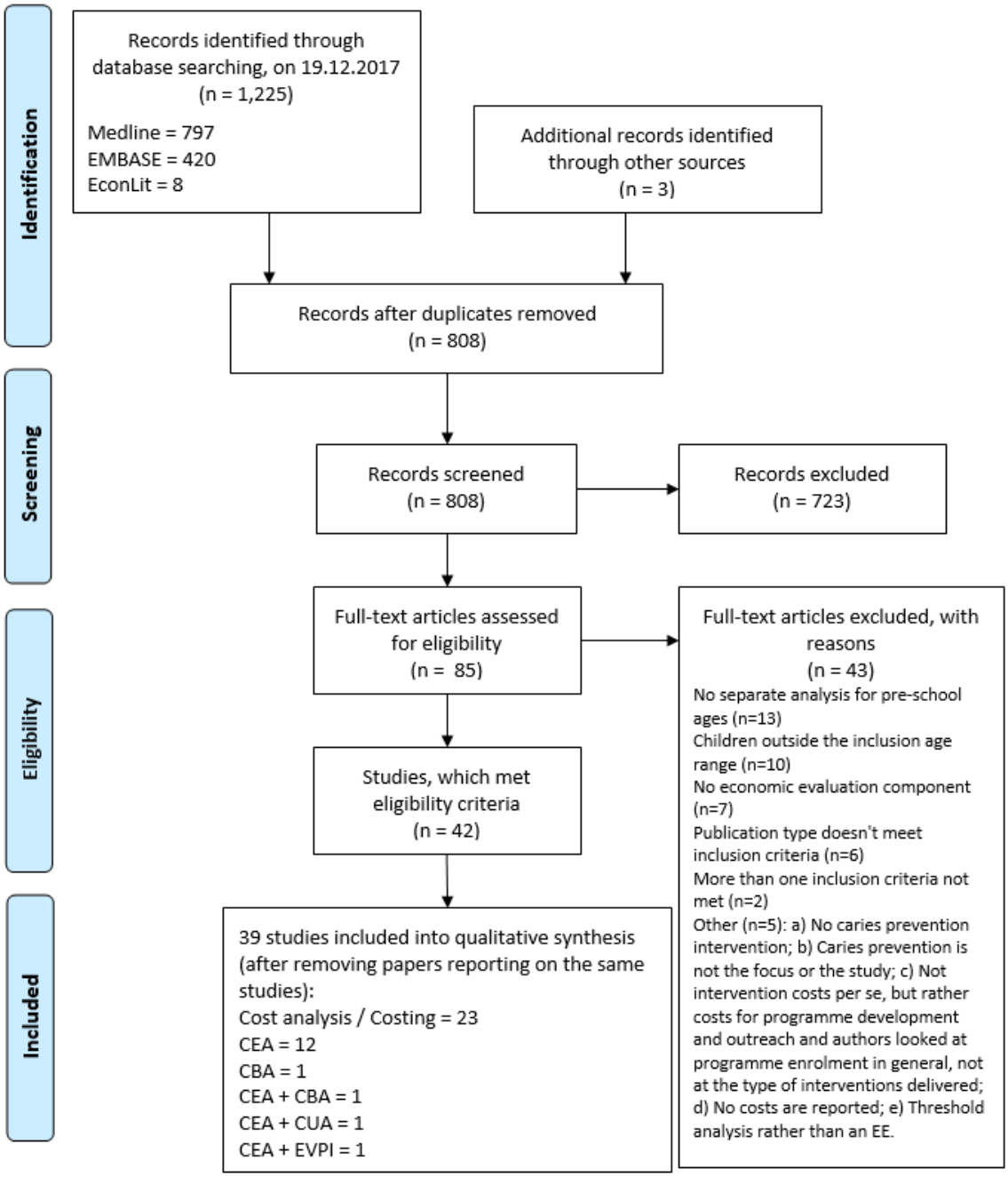

Figure 3.1 PRISMA flow diagram

Abbreviations: CBA, cost-benefit analysis; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; EVPI – expected value of perfect information analysis.

3.4.2 Study characteristics

Out of the thirty-nine papers, 25 (64%) were published between 2000 and 2017, inclusive. Twenty-three (59%) were partial EEs, namely cost analyses, and 16 (41.0%) were full EEs. Note, that the type of EE is reported in relation to the age group of interest: two to five years. There was one study which was a CBA for a full age range of participants (two to sixteen years), but only cost data were

reported for the two to seven year old group (Potapova 1977). This study was classified as partial economic evaluation, cost analysis. Figure 3.2 shows that the proportion of full EEs increased over time, starting from the 1980s onwards.

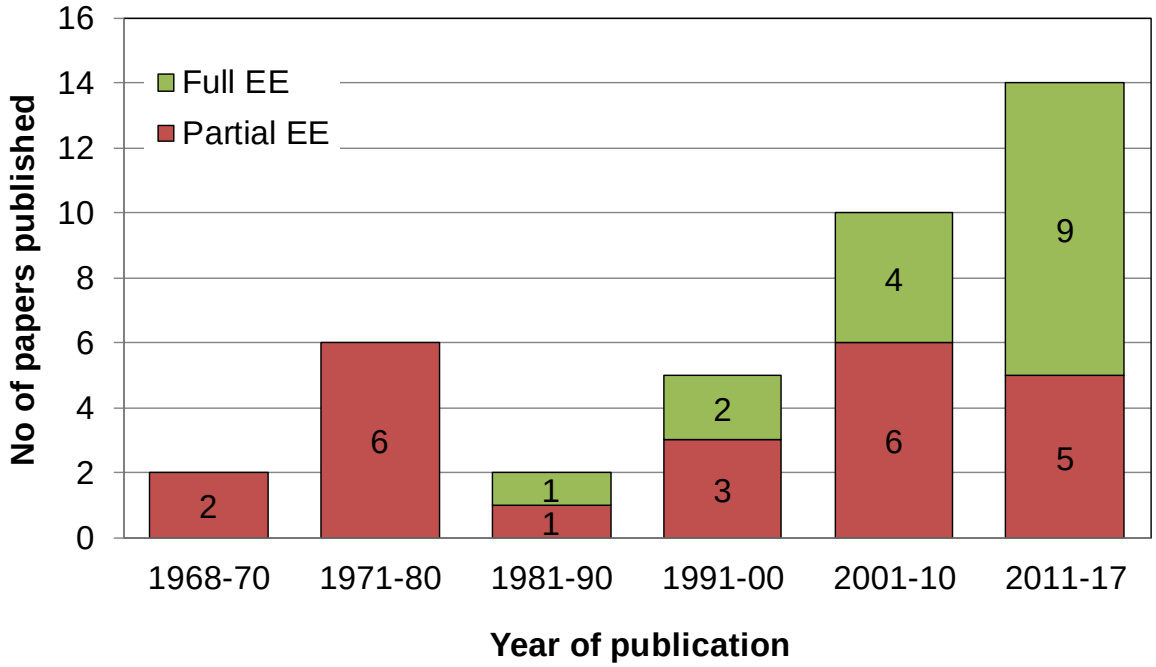

Figure 3.2 EEs by year of publication and type (full or partial EE)

Most studies were observational in nature (non-RCT / non-modelling study): 24 (61%), followed by evaluations alongside RCTs: 4 (10%), Markov models: 4 (10%) and simple calculations using previously published data (but not formal models): 3 (8%). Various other types of study design, such as decision-analytic modelling, system dynamics modelling, and evaluations based on RCT data (but not alongside an RCT), accounted for the remaining 10%.

Other main study characteristics are summarised in Table 3.2. The majority of studies were conducted in the USA: 16 (41%), followed by 9 (23%) in the UK, and 3 (8%) each in Canada and Sweden. The majority investigated multi-component interventions: 12 (31%), followed by water fluoridation: 7 (18%), oral health education (with or without additional elements): 4 (10%), and topical fluoride (varnish, foam, gel): 4 (10%). Cost analysis was the most frequently used type of economic evaluation: 23 (59%) followed by cost-effectiveness analysis (CEA): 12 (31%).

Table 3.2 Study characteristics – all included studies

Characteristic	No of studies (%) Total = 39
Year of publication:	
1968-70	2 (5%); 2 partial EEs
1971-80	6 (15%); 6 partial EEs
1981-90	2 (51%); 1 partial and 1 full EE
1991-00	5 (13%); 3 partial and 2 full EEs
2001-10	10 (26%); 6 partial and 4 full EEs
2011-17	14 (36%); 5 partial and 9 full EEs
Type of EE:	
Cost analysis *	23 (59%)
CEA	12 (31%)
CBA	1 (3%)
CEA + CBA	1 (3%)
CEA + CUA	1 (3%)
CEA + EVPI	1 (3%)
Type of study:	
Observational in nature (non-RCT / non-modelling study)	24 (61%)
Alongside an RCT	4 (10%)
Markov model	4 (10%)
Calculations using previously published data (but not a formal model)	3 (8%)
System Dynamics Modelling	2 (5%)
Based on an RCT, but not alongside it. (Costs of a hypothetical prevention programme, based on RCT results.)	1 (3%)
EVPI + cost-effectiveness model	1 (3%)
Study country:	
USA	16 (41%)
UK	9 (23%)
Canada	3 (8%)
Sweden	3 (8%)
Australia	2 (5%)
USSR	2 (5%)
Chile	1 (3%)
Finland	1 (3%)
Taiwan	1 (3%)
Uzbekistan	1 (3%)
Type of the intervention:	
Complex / multi-component intervention	12 (31%)
Water fluoridation	7 (18%)
Oral health education (with or without additional elements)	4 (10%)
Topical fluoride (varnish, foam, gel)	4 (10%)

Characteristic	No of studies (%) Total = 39
Multiple interventions compared	3 (8%)
Primary molar sealants	2 (5%)
Systemic fluoride (with or without additional elements)	2 (5%)
Toothbrushing	2 (5%)
Fluoridated milk and cereal	1 (3%)
Microbiological screening	1 (3%)
Preventive dental visit	1 (3%)

NOTE: CBA, cost-benefit analysis; CEA, cost-effectiveness analysis; CUA, cost-utility analysis; EVPI – expected value of perfect information analysis.

* One study (Potapova 1977) was a CBA for a full age range of participants, two to sixteen years, but only cost data were reported for the two- to seven-year-old group. For the purposes of our review this study was classified as partial economic evaluation, cost analysis.

3.4.3 Partial EEs

Twenty-three partial EE studies were reviewed in total. All partial EEs were cost analyses studies.

Interventions evaluated

Many of the partial EEs investigated the costs of water fluoridation: 7, or 30% of the total number of partial EEs (Ast et al. 1970, Lewis et al. 1972, Dowell 1976, Fidler 1977, Potapova 1977, Rugg-Gunn et al. 1977, Trubman et al. 1991). Six (26%) investigated multi-component interventions (Jong and Leske 1968, Lewis et al. 1977, Gisselsson et al. 1994, Kaakko et al. 2002, Jokela and Pienihakkinen 2003, Buckingham and John 2017). Three (13%) studies investigated topical fluoride (varnish, foam or gel) (Hawkins et al. 2004, Chen and Lin 2009, Kranz et al. 2014) and two (9%) compared multiple interventions (Hirsch et al. 2012, Edelstein et al. 2015). There were single studies investigating each of the following: fluoride drops (for younger children: two to four years old) and fluoride varnish (for older children: five to six years old) (Pashaev 1982), microbiological screening (for mutans streptococci) (Zavras et al. 2000), age at the first preventive dental visit (Savage et al. 2004), OH education of parents, with several additional components: fluoride tablets, toothbrushes and fluoride toothpaste (Wennhall et al. 2010), and supervised toothbrushing in nurseries

(Anopa et al. 2015). For further partial EE study description see Appendix 5 and Appendix 6, and for full EEs see Appendix 7 and Appendix 8.

Country of origin

Nine (39%) partial EE studies were conducted in the USA (Jong and Leske 1968, Ast et al. 1970, Trubman et al. 1991, Zavras et al. 2000, Kaakko et al. 2002, Savage et al. 2004, Hirsch et al. 2012, Kranz et al. 2014, Edelstein et al. 2015), followed by the UK – 5 (22%) studies (Dowell 1976, Fidler 1977, Rugg-Gunn et al. 1977, Anopa et al. 2015, Buckingham and John 2017) and Canada – 3 (13%) (Lewis et al. 1972, Lewis et al. 1977, Hawkins et al. 2004). Two studies (9%) were conducted in Sweden (Gisselsson et al. 1994, Wennhall et al. 2010) and two (9%) in the USSR (Potapova 1977, Pashaev 1982). There was one study (4%) from Finland (Jokela and Pienihakkinen 2003) and one (4%) from Taiwan (Chen and Lin 2009).

3.4.4 Full EEs

In the following sections the sixteen full EE papers will be classified by the country of origin, interventions evaluated, EE evaluation perspective, study settings, and type of EE used (CBA, CEA or CUA). The cost-effectiveness / cost-benefit results of these studies will be presented, and specific attention will be paid to the studies that investigated fluoride varnish applications.

Country of origin

Seven of the included full EE studies were conducted in the USA (44% of the total number of full EE studies) (Ramos-Gomez and Shepard 1999, Quinonez et al. 2006, Stearns et al. 2012, Chi et al. 2014, Ney et al. 2014, Samnaliev et al. 2015, Atkins et al. 2016); 4 (25%) in the UK (Donaldson et al. 1986, Davies et al. 2003, Kowash et al. 2006, O'Neill et al. 2017); 2 (12%) in Australia (Pukallus et al. 2013, Koh et al. 2015) and one (6%) each in Chile (Marino et al. 2007), Sweden (Widenheim and Birkhed 1991) and Uzbekistan (Ataniyazova et al. 2014).

Interventions evaluated

Six (37%) of the full EE papers investigated complex multicomponent interventions (Donaldson et al. 1986, Ramos-Gomez and Shepard 1999, Stearns et al. 2012, Ataniyazova et al. 2014, Samnaliev et al. 2015, O'Neill et al. 2017); three (19%) looked at OH education (with or without additional components) (Kowash et al. 2006, Pukallus et al. 2013, Koh et al. 2015); two (12%) – at primary molar sealants (Chi et al. 2014, Ney et al. 2014); and there was one study (6%) investigating each of the following: fluoridated milk and milk cereal (Marino et al. 2007), fluoride varnish (Quinonez et al. 2006), sodium fluoride tablets (plus other underlying interventions) (Widenheim and Birkhed 1991), toothbrushing (Davies et al. 2003), and comparing multiple interventions (Atkins et al. 2016).

EE evaluation perspective

In seven studies (44%) (Donaldson et al. 1986, Widenheim and Birkhed 1991, Ramos-Gomez and Shepard 1999, Davies et al. 2003, Kowash et al. 2006, Pukallus et al. 2013, Ataniyazova et al. 2014) the evaluation perspective was not stated; three studies (19%) used a Medicaid perspective (Quinonez et al. 2006, Stearns et al. 2012, Atkins et al. 2016); three (19%) employed a public payer perspective (Chi et al. 2014, Ney et al. 2014, O'Neill et al. 2017); a societal perspective was used in two evaluations (12%) (Marino et al. 2007, Koh et al. 2015); and one study (6%) used a combination of perspectives (base case analyses were conducted from the health care system and societal perspectives, subgroup analyses were conducted from a public payer perspective) (Samnaliev et al. 2015).

Settings

With regard to study settings, seven (44%) were modelling studies (Ramos-Gomez and Shepard 1999, Quinonez et al. 2006, Pukallus et al. 2013, Chi et al. 2014, Ney et al. 2014, Koh et al. 2015, Atkins et al. 2016); three (19%) were conducted in dental settings (dental practice, dental clinic) (Widenheim and Birkhed 1991, Samnaliev et al. 2015, O'Neill et al. 2017); two (13%) studies were conducted in

multiple settings (Donaldson et al. 1986, Stearns et al. 2012), two (13%) at home (Davies et al. 2003, Kowash et al. 2006); one study (6%) was kindergarten-based (Ataniyazova et al. 2014) and one (6%) community-based (Marino et al. 2007).

Type of EE used

The most frequently used type of full EE was CEA: 12 studies (75% of the total number of full EE studies) (Donaldson et al. 1986, Widenheim and Birkhed 1991, Ramos-Gomez and Shepard 1999, Davies et al. 2003, Quinonez et al. 2006, Marino et al. 2007, Stearns et al. 2012, Pukallus et al. 2013, Chi et al. 2014, Samnaliev et al. 2015, Atkins et al. 2016, O'Neill et al. 2017). Other studies employed CBA (Ataniyazova et al. 2014) or a combination of CEA with one of the following: CBA (Kowash et al. 2006), CUA (Koh et al. 2015) and expected value of perfect information (EVPI) (Ney et al. 2014) – one study used each method / method combination. Table 3.3 illustrates a further breakdown of the full EE studies by type of intervention and type of EE used.

Table 3.3 Full EE studies by type of intervention and type of EE used

Type of intervention evaluated	CEA	CBA	CEA + CBA	CEA + CUA	CEA + EVPI	Total
Complex / multicomponent interventions	5	1				**6**
Oral health education (with or without additional elements)	1		1	1		**3**
Primary molar sealants	1				1	**2**
Fluoridated milk & cereal	1					**1**
Fluoride tablets (with other underlying interventions)	1					**1**
Fluoride varnish	1					**1**
Multiple interventions compared	1					**1**
Toothbrushing	1					**1**
Total	**12**	**1**	**1**	**1**	**1**	**16**

Cost-effectiveness analyses (CEAs)

Twelve studies employed CEA. Half of these CEA studies were conducted in the USA (Ramos-Gomez and Shepard 1999, Quinonez et al. 2006, Stearns et al. 2012, Chi et al. 2014, Samnaliev et al. 2015, Atkins et al. 2016), three (25%) were from the UK (Donaldson et al. 1986, Davies et al. 2003, O'Neill et al. 2017), and there was one study (8%) from each of these three countries: Australia (Pukallus et al. 2013), Chile (Marino et al. 2007) and Sweden (Widenheim and Birkhed 1991).

Five studies (42%) evaluated complex interventions, which included multiple components (for example, a combination of fluoride varnish/gel application, fissure sealants, OH education, and provision of toothpaste and toothbrushes), and/or multiple levels of interventions (e.g. minimal, intermediate and comprehensive) (Donaldson et al. 1986, Ramos-Gomez and Shepard 1999, Stearns et al. 2012, Samnaliev et al. 2015, O'Neill et al. 2017). Additionally, there were individual studies on the following: 1) Sodium fluoride tablets (plus annual dental care from three years old, basic preventive programme: FVA once a year, including weekly mouth rinsing with NaF solution from six years old, and fluoride varnish once a year; high caries risk individuals received tailored preventive care; it was assumed that all children used fluoride toothpaste daily at home from at least four years of age) (Widenheim and Birkhed 1991); 2) Postal programme: fluoride toothpaste and information leaflet encouraging twice daily supervised TB (four times a year) and toothbrush (once a year) (Davies et al. 2003); 3) Fluoride varnish applications (Quinonez et al. 2006); 4) Fluoridated milk and milk-cereal (Marino et al. 2007); 5) Telephone OH education programme, toothbrushes and toothpaste posted to home addresses, with underlying water fluoridation (Pukallus et al. 2013); 6) Primary molar sealant strategies (Chi et al. 2014); and 7) Multiple interventions were compared: a) water fluoridation, b) dental sealants, c) fluoride varnish applications, d) home tooth brushing with fluoride toothpaste, and e) conducting initial dental exams on children less than 18 months of age with parents receiving parental counselling (Atkins et al. 2016).

Other types of full EE analyses

Three studies used a combination of CEA and one other type of economic analysis. A British study used a combination of CEA and CBA (Kowash et al. 2006). The intervention was dental health education (diet and oral hygiene): there were four intervention groups with varied intensity and components included. One study conducted in Australia used a combination of CEA and CUA (Koh et al. 2015). This was the only study included in the review that used a preference-based instrument to obtain QALY as an outcome measure, namely, the Child Health Utility 9 Dimensions (CHU9D) parental proxy questionnaire. This study evaluated the cost-effectiveness of a home-visit intervention conducted by oral health therapists relative to a telephone-based alternative and no intervention. The authors used Markov modelling methods and the CHU9D data were collected from a consecutive sample of 100 parents who presented to a community paediatric dental clinic with their children aged 5 years and younger with caries, within a specified two-month period. And, finally, an American study employed a combination of CEA and expected value of perfect information (EVPI) approach (Ney et al. 2014). The authors compared two primary molar sealant strategies: a) always seal; b) standard care.

There was one study that employed CBA only (Ataniyazova et al. 2014). This study was conducted in Uzbekistan and investigated a kindergarten-based combined hand hygiene and OH promotion intervention. OH promotion included distribution of toothpaste, toothbrushes and OH education materials. The authors used various sources for their benefit-related data such as governmental statistics published reports, WHO and the International Monetary Fund databases, as well as household data based on a cross-sectional survey of kindergarten-age children. Cost of illness approach was used to calculate intangible costs. The results were presented as both net benefit per child and cost-benefit ratio.

A wide variety of oral health outcome measures were used in the reviewed full EE studies (Table 3.4). Four studies (Donaldson et al. 1986, Davies et al. 2003, Marino et al. 2007, Koh et al. 2015) used mean dmft and/or dmfs. Two studies used conversion from caries-free to caries-active (plus other secondary

measures) (Kowash et al. 2006, O'Neill et al. 2017). Nine other OH outcome measures were used in one study each. Five different cost-effectiveness outcomes were used in individual studies. Only one study used the quality-adjusted life year (QALY) as an outcome (Koh et al. 2015). The most widely used options for reporting of costs and outcomes were the incremental cost-effectiveness ratio (ICER) and the average cost-effectiveness ratio (ACER).

Table 3.4 Full EE studies: oral health and economic outcomes used, and reporting and presentation of costs and outcomes

Characteristic	No of studies (%) Total = 16	Study references
Oral health outcomes:		
dmft or/and dmfs	4 (25%)	(Donaldson et al. 1986, Davies et al. 2003, Marino et al. 2007, Koh et al. 2015)
Conversion from caries-free to caries-active (plus other secondary measures)	2 (12%)	(Kowash et al. 2006, O'Neill et al. 2017)
Cavity-free months	1 (6%)	(Quinonez et al. 2006)
fs, dfsa	1 (6%)	(Widenheim and Birkhed 1991)
Mean No of restorations and extractions averted	1 (6%)	(Ney et al. 2014)
Number of carious surfaces	1 (6%)	(Ramos-Gomez and Shepard 1999)
Number of carious teeth	1 (6%)	(Pukallus et al. 2013)
Number of cases / incidence rates of caries and stomatitis	1 (6%)	(Ataniyazova et al. 2014)
Rates of dental treatment	1 (6%)	(Stearns et al. 2012)
Reduction in dental treatments	1 (6%)	(Samnaliev et al. 2015)
Reduction in No of carious teeth; reduction in full mouth dental reconstructions	1 (6%)	(Atkins et al. 2016)
N/A (tooth-level model)	1 (6%)	(Chi et al. 2014)
Preference-based outcomes:		
QALY (based on Child Health Utility 9 Dimensions (CHU9D) - parental proxy questionnaire)	1 (6%)	(Koh et al. 2015)
Reporting and presentation of costs and outcomes:		
ICER	7 (44%)	(Quinonez et al. 2006, Marino et al. 2007, Stearns et al. 2012, Pukallus et al. 2013, Ney et al. 2014, Koh et al. 2015, O'Neill et al. 2017)
ACER *	3 (19%)	(Widenheim and Birkhed 1991, Kowash et al. 2006, Atkins et al. 2016)
B/C ratio *	2 (12%)	(Kowash et al. 2006, Ataniyazova et al. 2014)
Cost per carious surface averted, cost saving threshold	1 (6%)	(Ramos-Gomez and Shepard 1999)
Cost per event avoided (tooth is not restored or extracted)	1 (6%)	(Chi et al. 2014)
Cost per incremental change in dmfs	1 (6%)	(Donaldson et al. 1986)

Characteristic	No of studies (%) Total = 16	Study references
Cost per tooth saved, cost per child saved from caries experience, cost per child saved from extraction experience	1 (6%)	(Davies et al. 2003)
Number of avoided (reduced) restorative or surgical treatment visits in the ambulatory dental clinic or operating room at the hospital	1 (6%)	(Samnaliev et al. 2015)

NOTE: * One study (Kowash et al. 2006) reported both average C/E and B/C ratios.

Cost-effectiveness / cost-benefit results

Six out of 15 studies that employed CEA concluded that the intervention under evaluation was cost-effective compared to the comparison. The interventions were: a complex dental disease management programme (Samnaliev et al. 2015), OH education programmes (Kowash et al. 2006, Pukallus et al. 2013, Koh et al. 2015), fluoridated milk and milk-cereal (Marino et al. 2007), and a study with five different caries prevention interventions compared (Atkins et al. 2016). In four cases the intervention was cost-effective for certain sub-groups or for certain scenarios, but not the others (Donaldson et al. 1986, Widenheim and Birkhed 1991, Ramos-Gomez and Shepard 1999, Stearns et al. 2012). In two studies on primary molar sealants the 'always seal' intervention was more effective, but more costly than standard care (Chi et al. 2014, Ney et al. 2014). Two studies on fluoride varnish indicated that the intervention was not cost saving (Quinonez et al. 2006, O'Neill et al. 2017). The authors of a postal toothbrushing programme evaluation (Davies et al. 2003) did not draw any conclusions on its cost-effectiveness.

Of the two studies that employed CBA, one study showed that benefits of a combined hand hygiene and OH promotion programme outweighed costs at each discount rate level considered (Ataniyazova et al. 2014). The other study compared dental health education with several other caries prevention strategies (Kowash et al. 2006). The results showed that the dental health education programme had better cost-benefit ratios than other preventive programmes.

The only study that used QALY as one of the outcomes, evaluated the cost-effectiveness of a home-visit intervention conducted by oral health therapists

relative to a telephone-based alternative and no intervention (Koh et al. 2015). The home visits and telephone interventions resulted in 7 and 6 QALYs, respectively, gained over the usual care group for the 100 children over 5.5 years. Both interventions were dominant, as they saved costs and produced health benefits over usual care.

Studies investigating fluoride varnish applications

Of particular interest are studies that investigated the cost-effectiveness of fluoride varnish applications (FVAs), as the PT@3 trial, discussed in detail in further chapters, examined the cost-effectiveness of FVA over and above supervised nursery toothbrushing and other Childsmile components (treatment is usual).

Two CEA studies on FVA were identified. One was a British RCT-based evaluation conducted in NHS general dental practices (O'Neill et al. 2017) and the other was a USA-based Markov modelling study on Medicaid-enrolled children receiving interventions during Well-child visits at a medical centre during primary care (Quinonez et al. 2006). The primary OH outcome measure used in the O'Neill et al study was conversion from caries-free to caries-active states, while dmfs and dmft in children with caries, number of episodes of pain and number of extractions were used as secondary outcome measures. Caries severity (dmfs) was also calculated for the whole sample. The authors used the following cost-effectiveness measures: ICERs for three outcome measures: caries-free status, carious surfaces, and episodes of pain; and net monetary benefit. The American study used cavity-free months as their OH outcome measure, and ICERs (cost per cavity-free month, cost per treatment averted) as cost-effectiveness measures.

The results of both studies indicated that the interventions were not cost saving. O'Neill and colleagues concluded that the costs of providing the preventive intervention outweighed savings in treatment over the three-year follow-up period. The intervention delivered in general dental practice was unlikely to produce a cost-saving for the NHS. Even with their evidence-based intervention and high levels of adherence, over a third of children developed caries. Quinonez et al established that, based on their assumptions, fluoride varnish use

in the medical setting was effective in reducing early childhood caries in low-income populations but was not cost saving in the first 42 months of life. They advised that evaluations using a longitudinal cohort were needed.

Appendix 7 and Appendix 8 contain further full EE study descriptions.

3.4.5 Results of reporting quality assessment of full EEs

The results of the assessment of full EE studies using the CHEERS checklist showed substantial variation in reporting quality. Figure 3.3 shows the proportion of studies that did not meet each criterion, i.e. scored zero on a particular item. Not every single item was applicable to every study. The items that were most often unmet were: #20a – Characterising uncertainty (for single study-based EEs), with 67% of all studies to which this item was applicable not meeting this criterion; #6 – Study perspective, with 44% of studies not meeting this criteria; #18 - Study parameters: 38% not met; and #13a - Estimating resources and costs (for single study-based EEs): 33% not met. Several items were met by all studies to which these items were applicable: items 1 and 2 – Title and Abstract, #10 - Choice of health outcomes; #11a and #11b - Measurement of effectiveness (for single study-based and model-based EEs, respectively); #13b - Estimating resources and costs (model-based EEs); #15 - Choice of model; #16 – Assumptions (model); and #21 - Characterising heterogeneity (applicable to two studies only). Item 12 – Measurement and valuation of preference-based outcomes was applicable to one study only and was met. Scores by item by study are shown in Appendix 9.

The overall CHEERS score for each reviewed study is shown in Figure 3.4. The studies are ordered in chronological order. It is noteworthy that more recent papers were of higher reporting quality than earlier ones.

Papers published from 2014 onwards met 100% of applicable CHEERS items. For all 16 papers combined the median proportion of all applicable CHEERS items met was 97.5% and the mean was 81.8%. The range was 50% to 100%. With regards to “Other” items (not shown in Figure 3.3 and not included in the total score in Figure 3.4), only three papers (19%) provided information on their

authors' conflict of interest, while nine papers (56%) indicated a source of funding.

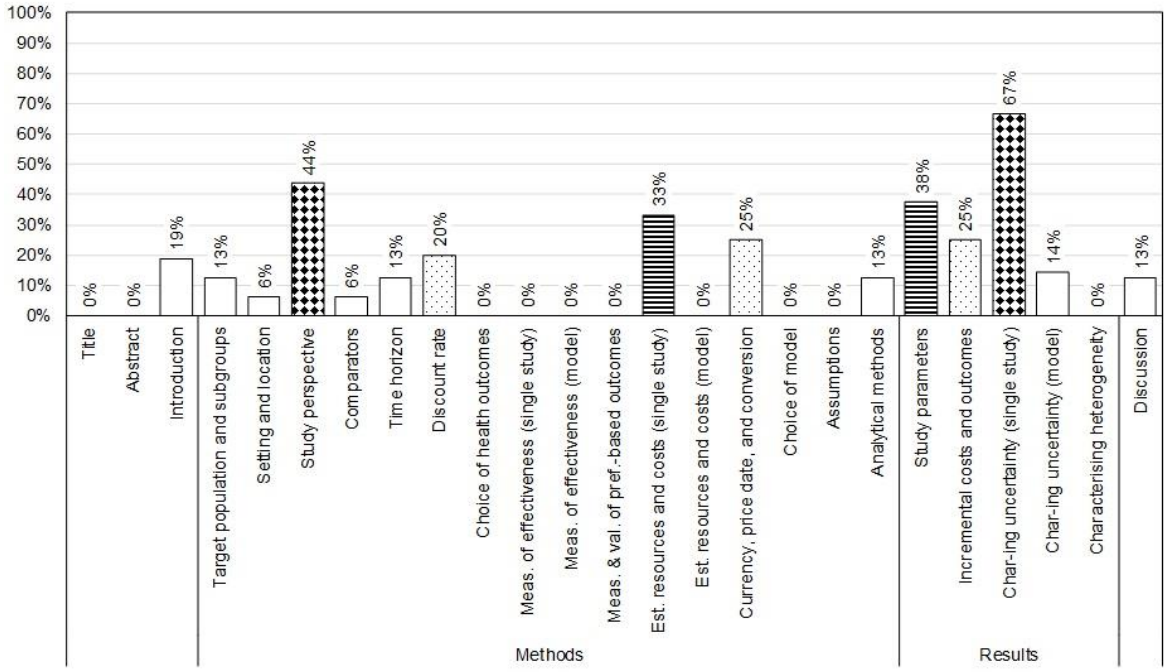

Figure 3.3 Proportion of CHEERS items not met, by item

Key: Chequered fill – over 40% of eligible studies did not meet a criterion; Horizontal lines fill – 30% < 40% not met; Dotted fill – 20% < 30% not met; White – < 20% not met.

Notes: 1) The total (100%) was different for various items, as some items were not applicable to all studies. 2) "Other" items, namely "Source of funding" and "Conflicts of interest" were not included when rating the reporting quality of the reviewed papers.

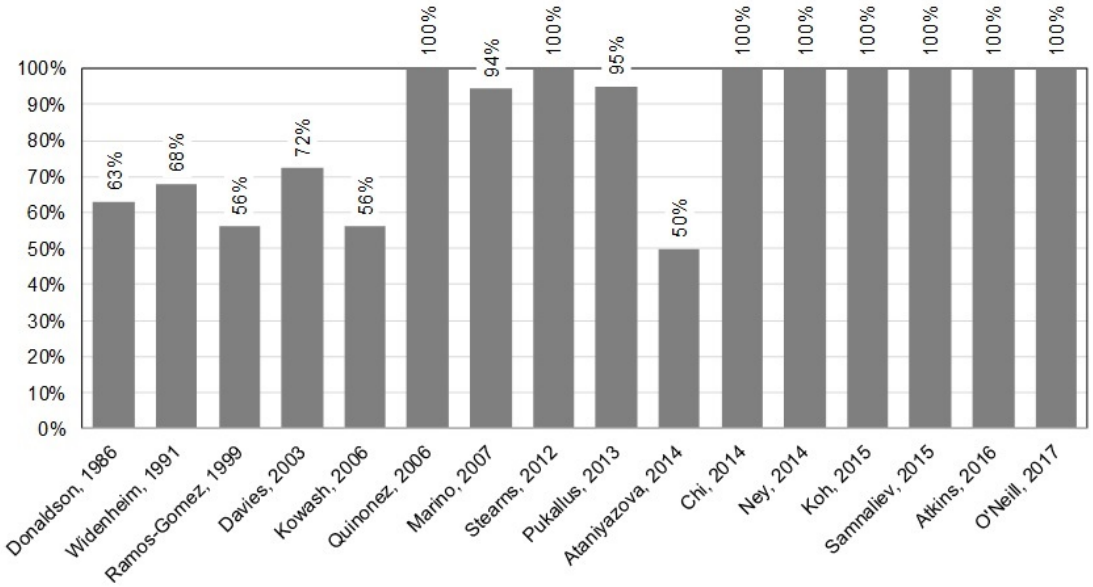

Figure 3.4 CHEERS score for each reviewed full EE study (% of total applicable items)

3.5 Discussion

This is the first systematic review to focus on the EEs of OH improvement interventions targeted at the early life. This period has been shown to be crucial in influencing health in later years (Colak et al. 2013, ICOHIRP 2015), as well as having a potential to generate significant long term returns (Public Health England 2016c, York Health Economics Consortium 2016e) with early prevention interventions in place.

It is noteworthy that more recent papers were of higher reporting quality than earlier ones. The proportion of full EEs increased over time, starting from the 1980s onwards. This can be explained by the rise of health economics as a discipline and the publication of key texts on the matter, for example (Mooney and McGuire 1988, Mooney 1992, Drummond and Jefferson 1996, Gold et al. 1996).

The most widely used type of analysis were cost analysis and CEA, which is similar to the findings of a recent systematic review of EEs in wider child OH research (Rogers et al. 2019). Over 60% of the reviewed papers were published between 2000 and 2017, inclusive. The majority of studies were conducted in the USA and the UK, were of observational design, or evaluations alongside RCTs and Markov models. Just under a third of the studies reviewed investigated complex multi-component interventions, and approximately a fifth focused on water fluoridation.

Unlike the previous reviews (Marino et al. 2013, Tonmukayakul et al. 2015), the current review did not find a mismatch between the study descriptor and actual type of analysis used. All studies that were labelled a CEA or a CBA or a combination of methods were indeed those study types. This may be explained by the fact that the vast majority of full EEs in the field of interest were published relatively recently, by which time guidance on EE methods was established and widely used, such as (Drummond and Jefferson 1996, Siegel et al. 1996, Evers et al. 2005, Philips et al. 2006, Husereau et al. 2013b).

Although the reporting quality of partial EEs was not formally assessed in the systematic review, some parameters, which were included in the data extraction template, indicate that, on the whole, partial EEs were inferior to full EEs in relation to reporting these parameters. For example, over half of the reviewed partial EEs did not employ sensitivity analysis, whereas three quarters of full EEs studies did. The majority of full EEs stated the discount rate used, whereas only three partial EE studies did so. Additionally, a higher proportion of full EE papers indicated the baseline year for their analysis. Previous reviews identified similar methodological limitations, namely: absence of sensitivity analysis, limited information on adjustments for discounting, and not reporting the base year (Marino et al. 2013, Tonmukayakul et al. 2015, Hettiarachchi et al. 2018, Rogers et al. 2019). A significant proportion of the papers did not state the perspective used in the analysis: 83% of partial EEs and 44% of all full EEs, which is similar to the results of a previous systematic review of CUAs of OH interventions (Hettiarachchi et al. 2018).

The review identified 16 full EEs, which used a variety of OH outcome and economic outcome measures. This variation makes it challenging to compare the cost-effectiveness of individual caries prevention interventions. This concurs with the conclusions of two previous systematic reviews (Hettiarachchi et al. 2018, Rogers et al. 2019). Interpretation of cost-effectiveness ratios for dental health outcomes is similar to the standard challenges of using CEA when comparing different outcomes. Without the use of an accepted threshold for a generic outcome, such as a QALY (as discussed in Chapter 2, Section 2.5.2.1), comparability is not possible. It is not clear how much the payer (e.g. a health care system, public payer or society) is willing to pay per decayed surface/tooth avoided, or per child kept caries-free (Lord et al. 2015). Only one study used a preference-based health-related quality of life measure that allows calculation of QALY as one of the outcomes, which, in turn, allows a comparison of cost-utility results of various interventions' evaluations. This lack of evidence reveals a clear gap in relation to preschoolers' OH research.

Over 40% of the reviewed full EE papers concluded in favour of the intervention(s) under investigation. However, there were small numbers of studies investigating each intervention type (e.g. fluoride varnish, OH education,

dental sealants, toothbrushing, fluoridated food and drinks, water fluoridation). The studies were underpowered (Kowash et al. 2006, Pukallus et al. 2013, Koh et al. 2015), used simple spreadsheet-based calculations (Marino et al. 2007, Ataniyazova et al. 2014, Atkins et al. 2016), or were pilot studies (Samnaliev et al. 2015) making it challenging to draw reliable conclusions with regard to the value of primary caries prevention.

The only full EE conducted alongside a well powered randomised controlled trial and deemed to be of high reporting quality, was O'Neill et al. (2017), which compared a combined fluoride intervention (fluoride varnish; free toothbrush and fluoride toothpaste and standardized prevention advice) to the control group (advice only) in general dental practice settings. It was found that the mean cost per carious surface avoided after three years was £251 (95% CI £454, £79). ICERs were reported for three outcome measures: caries-free status, carious surfaces, and episodes of pain; and for total costs were as follows: -£2,070, -£249 and -£264, respectively (the negative ICER should be interpreted as the mean additional cost per outcome avoided). A positive net monetary benefit was found only with respect to carious surfaces: if society were willing to pay £1,000 per carious surface avoided, the intervention would deliver a net monetary benefit of approximately £1,063 (95%CI £298, £1,855) per carious surface. The authors concluded that the costs of providing a combined fluoride intervention outweighed savings in treatment over the three-year follow-up period. This intervention was unlikely to produce a cost-saving.

The results of the quality assessment of full EEs using the CHEERS checklist showed substantial variation in reporting quality. The items most often unmet were: ‘characterising uncertainty’, ‘study perspective’, ‘study parameters’, and ‘estimating resources and costs’. Of note, more recently published papers were of higher reporting quality. CHEERS is the most recently developed EE checklist that was created to update previous guidelines (Husereau et al. 2013b, Frederix 2019). It has been widely used as a single tool for assessing the quality in systematic reviews of EE studies, including some focusing on oral health (Geisler et al. 2017, Hettiarachchi et al. 2018).

One of the limitations of this systematic review is that due to the time constraints only 20% of randomly selected records were assessed or checked independently by a second reviewer, whereas according to best practice advice (Higgins and Green 2011, Thielen et al. 2016, van Mastrigt et al. 2016), it is recommended that all steps critical for study selection, data extraction and risk of bias assessment should be done by two reviewers independently. Another limitation is that the reporting quality was only formally assessed for full EE studies. The CHEERS checklist cannot be meaningfully used for partial EEs assessment, as many of the items are not applicable. Additionally, the overall methodological quality of the reviewed studies was not formally assessed.

3.6 Conclusion

A limited number of EEs of primary caries prevention in 2-5-year-olds was identified (n=39), with an even smaller number of full EE studies (n=16). The studies were of varying reporting quality and many of them had methodological flaws.

Although the number of EE studies relating to OH improvement interventions in preschoolers has been increasing in recent years, a number of items were inadequately reported in a substantial proportion of the reviewed studies. The review has highlighted wide variation in: a) types of caries prevention interventions investigated; b) effectiveness measures used; c) how costs and outcomes are reported; and d) study perspective (when indicated).

Importantly, only one study employed CUA, using a preference-based outcome measure. This notable lack of use of preference-based health-related quality of life measures in the field of preschoolers' OH likely reflects the challenges with conducting EE in this young age group, the availability of suitable preference-based measures, and also flags up the limitations with the use of these studies for the purposes of decision making in dental healthcare.

While variation in prevention interventions investigated is entirely expected, the methodological limitations identified preclude meaningful comparisons across studies as well as compromise the evidence base for strategies in relation to the

prevention of this disease in this age group. Due to small numbers of studies investigating each intervention type and questionable methodological quality of many of the reviewed EEs it was not possible to arrive at reliable conclusions with regards to the economic value of primary caries prevention.

With dental caries being one of the most common diseases affecting humans worldwide the identification of cost-effective prevention strategies in children should be a global public health priority. This agrees with the recommendations in the recent articles outlining the challenges and priorities for global OH. In order for this to be achieved, studies should be designed to include economic evaluations using best practice methods guidance and adhering to standards for reporting and presenting. Such improvements to the evidence base will serve to increase both the availability and quality of economic evidence in this important area.

Chapter 4 Instruments for measuring general and oral health-related quality of life in three- to five-year-old children

4.1 Introduction to Chapter 4

Following from Chapter 3's systematic review of economic evaluations of primary caries prevention in preschool children, this chapter will review the existing instruments (questionnaires) for measuring health-related quality of life (HRQoL) in children aged three to five years. Two groups of HRQoL measures will be reviewed separately: the generic HRQoL instruments (which are called here general health-related quality of life (GHQoL)) and oral health-related quality of life (OHQoL) instruments. The chapter will start with introducing the concepts of HRQoL/GHQoL and OHQoL, and then will cover the use of HRQoL measures in clinical trials. The aims and methods of the reviews will be presented as well as the results of the two separate reviews: of GHQoL and OHQoL instruments. The results will be discussed in the context of previous research and previously published systematic reviews.

It is recommended to include a range of HRQoL measures (a preference-based and a non-preference-based GHQoL measures, and a condition-specific measure), when conducting EEs of clinical trials, as they perform different tasks (Drummond 2001, Raat et al. 2006). This chapter identifies suitable GHQoL and OHQoL questionnaires to be used in the Protecting Teeth @ 3 (PT@3) trial.

4.1.1 Health-related quality of life

Various definitions of health-related quality of life (HRQoL) exist, with at least four having been identified in the literature (Karimi and Brazier 2016). According to the UK's National Institute for Health and Care Excellence (NICE) glossary, HRQoL is "a combination of a person's physical, mental and social well-being; not merely the absence of disease" (NICE 2020b).

The importance of understanding the impact of disease and treatment on child HRQoL is recognised. HRQoL is a complex, multidimensional concept, including social, emotional and physical functioning or well-being, related to the patient's

health state. This increased recognition has given rise to a growing use of child self-report and proxy-report instruments in paediatric clinical trials (Germain et al. 2019). Although there is a consensus that self-report should always be used where possible (Marshman et al. 2015), proxy reports are considered to be a valuable way of obtaining information about children whose age or cognitive/health status prevents them from reliably self-reporting (Eiser and Morse 2001, Germain et al. 2019). It is generally accepted that children under the age of five cannot provide reliable self-reports, and that proxy reports should be used (Wallander et al. 2001, Varni et al. 2007, Matza et al. 2013). For babies, infants and preschoolers who are unable to self-report, proxy reports are unavoidable. However, the issues surrounding proxy reports have been recognised and investigated by numerous authors who point out that conclusions from individual studies are contradictory (Germain et al. 2019).

Measurement of HRQoL in young children (under six years of age) is challenging as motor and cognitive development is rapid, and measurement of HRQoL needs to take into account the changes which emerge with this development (Bradlyn et al. 1996, Verstraete et al. 2020b).

4.1.2 Oral health-related quality of life

Historically, traditional methods of measuring oral health and treatment needs were based mainly on clinical indicators (FDI 2015). However, these indicators do not necessarily account for the functional and psychosocial aspects of oral health, and they do not reflect people's perceptions and concerns about their oral health. Oral health-related quality of life (OHQoL) measures have been developed to determine the extent to which oral conditions affect individual's behaviour and social functioning. They complement the conventional clinical measures of oral health. Together with clinical and behavioural indicators OHQoL measures used in assessments of oral healthcare needs of populations provide a comprehensive approach to planning oral health services. OHQoL measures are essential outcomes to determine the cost-effectiveness of oral care and oral treatments as well as of public health interventions (FDI 2015). Assessment of OHQoL outcomes is recognised by oral healthcare researchers and policymakers as vital to planning oral healthcare programmes (Allen 2003).

Similarly to HRQoL, there are several definitions of OHQoL (Locker and Allen 2007). For example, the World Dental Federation (FDI) defines OHQoL as “a multidimensional construct that reflects (among other things) people's comfort when eating, sleeping, and engaging in social interaction; their self-esteem; and their satisfaction with respect to their oral health” (Bennadi and Reddy 2013, FDI 2015).

OHQoL plays an important role in understanding subjective patient evaluations of and experience with oral healthcare. Incorporating OHQoL creates a shift from traditional medical and dental criteria to assessment and care that focus on a person's social and emotional experience and physical functioning. Thus, OHQoL measurement has the potential to enhance evaluation, clinical research and care in a number of ways, including needs assessment of a population or a specific clinical group. OHQoL assessment can also be used as an outcome measure across specialty areas, including paediatric caries research. OHQoL provides a unique perspective on dental care from the child participant or from an observer like a parent (Genderson et al. 2013).

Caries in preschoolers can have detrimental effects. For example, it can lead to discomfort and pain, infections and difficulties with eating, maintaining optimal weight, sleeping and socialising (Nora et al. 2018). It can have a negative impact on physical, social, and emotional aspects, thus affecting a child’s general and oral health and child and family quality of life (White 2017, Nora et al. 2018, Phantumvanit et al. 2018). A recent systematic review and meta-analysis demonstrated an association of dental caries with a negative impact on OHQoL of preschool children, irrespective of the caries severity: the presence of at least one dmft (teeth decayed, missing due to decay, and filled teeth) was sufficient to increase values of the OHQoL indices (Nora et al. 2018).

This chapter clearly distinguishes between the generic HRQoL, which is called here general health-related quality of life (GHQoL), and OHQoL. This chapter includes two reviews: a) of GHQoL measures, and b) of OHQoL measures.

4.1.3 Using health-related quality of life measures in clinical trials

There are different types of HRQoL instruments (Hettiarachchi et al. 2019). Generic HRQoL instruments are designed for different types of disease and different patient populations (Drummond et al. 2005c). These are comprehensive measures of HRQoL that are widely used and have established validity and reliability across different disease conditions and patient populations. As was mentioned in Chapter 2, Section 2.5.2.4, earlier, disease-specific HRQoL instruments are designed to assess the quality of life concerning specific diseases, medical conditions, or patient populations (Whitehead and Ali 2010). The generic and disease-specific instruments that are developed based on classification systems and preferences weights are known as preference-based. These preference-based instruments are used in cost-utility analysis (Drummond et al. 2005c).

Figure 4.1 further illustrates different types of HRQoL measures that can be used in a clinical trial. The different types of measures have different advantages: for example, a disease- or condition-specific scale may have the maximum responsiveness to change, whereas a 'utility' or preference-based measure may have the potential to influence public policy and resource allocation decisions by allowing the results of the trial to be compared with the results of other trials across various disease areas, as it enables quality adjusted life years (QALYs) to be calculated (Drummond 2001).

When conducting economic evaluations of clinical trials, it is recommended to include the full range of HRQoL measures, on the grounds that they perform different tasks. However, concerns about the measurement burden to the respondent should also be taken into account and choices between the measures have to be made sometimes (Drummond 2001).

Bearing this recommendation in mind, the aim of this chapter of the thesis was to identify suitable questionnaires to be used in the Protecting Teeth @ 3 (PT@3) trial prior to the commencement of the economic evaluation, namely: a) a preference-based GHQoL measure; b) a non-preference-based GHQoL measure,

and c) an OHQoL, "condition"-specific, measure. More information on the PT@3 trial can be found in Chapter 5, Section 5.2.

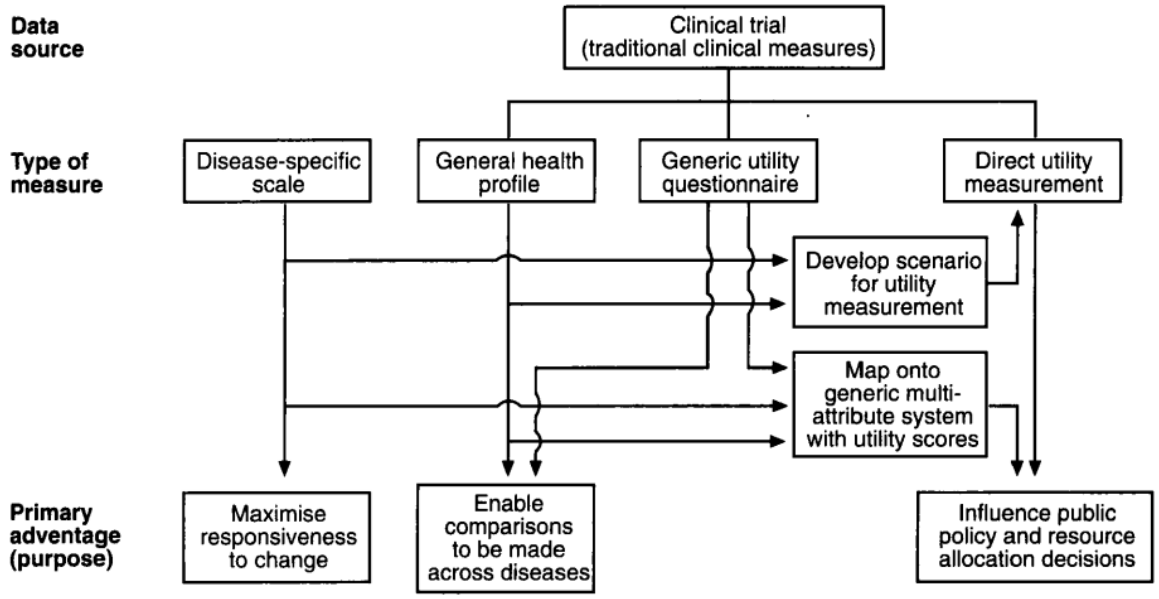

Figure 4.1 Interrelationships between health-related quality of life measures
(Source: Drummond, 2001)

The children in the PT@3 Study were three to five years old, therefore the aim of this review was to identify GHQoL and OHQoL instruments that could be used in this younger child age group. As elicitation of answers from preschoolers requires a face to face interview (Germain et al. 2019), which, in turn, is considerably time intensive, and because, as was mentioned earlier in Section 4.1.1, children under the age of five cannot provide reliable self-reports, the search target were parental proxy questionnaires on the child's GHQoL that can be self-administered by the parent/guardian of the child.

This chapter presents the aims, research methods, and results of a non-systematic literature review of GHQoL and OHQoL questionnaires used in preschool children aged three to five years. The review was conducted in order to identify suitable GHQoL and OHQoL instruments to be used in the Protecting Teeth @ 3 (PT@3) randomised controlled trial.

4.2 Aims

The main purpose of the quality of life instruments review was to answer the following research question:

> What are the existing GHQoL and OHQoL instruments for the age group three to five years? And which of these are best suited to be used in the Protecting Teeth @ 3 randomised controlled trial, which investigates the effectiveness and cost-effectiveness of fluoride varnish application in nursery settings?

The specific objectives of this quality of life instruments review were as follows:

1) To identify, assess and provide descriptive characteristics of the existing GHQoL instruments that have been developed for three- to five-year old children, except for the GHQoL instruments that were developed specifically for children with chronic conditions. Both proxy- and child self-report measures were to be included, but parental proxy questionnaires on the child's GHQoL that could be self-administered by the parent/guardian of the child were the main target.

2) To identify, assess and provide descriptive characteristics of the existing OHQoL instruments that that have been developed for three- to five-year old children. Both proxy- and child self-report measures were to be included, but parental proxy self-administered questionnaires were the main target.

3) To produce descriptive tables comparing the identified GHQoL and OHQoL instruments.

4) On the basis of the above, to provide recommendations on which GHQoL and OHQoL instruments would be best to be used in the PT@3 trial.

4.3 Methods

A snowball approach for identifying relevant papers was used. Snowballing is using the reference list of a paper or the citations to the paper to identify additional papers (Wohlin 2014). In the initial exploratory stage, systematic and non-systematic reviews of GHQoL and OHQoL instruments were found and examined.

The reviews were searched for using Medline (via the Ovid platform) and Google Scholar. During the development of the search strategies and terms, help was sought from a University of Glasgow subject librarian, a health economist and oral health experts. The reference lists of the identified reviews were checked for any earlier reviews. The following blocks of search terms were used for GHQoL instruments:

1) Construct of interest: quality of life.
2) Child age: infant, toddler, preschool, kindergarten.
3) Title or keywords had to include “review” or “systematic review”.

GHQoL instruments that were developed specifically for children with chronic conditions were excluded from the results of the search. The search and screening of reviews was stopped once there were no new GHQoL instruments identified within the most recently screened reviews.

The search terms for OHQoL instruments were as follows:

1) Construct of interest: quality of life.
2) Child age: infant, toddler, preschool, kindergarten.
3) Oral health terms, e.g. oral health, dental, caries, etc.
4) Title or keywords had to include “review” or “systematic review”.

Two Excel spreadsheets containing identified GHQoL and OHQoL instruments were created. The spreadsheets contained the following columns: name of the instrument, country of origin, child age, and the previous systematic review source, where the instrument was initially found (author, year).

The next step was contacting experts for external validation. The contacted experts can be classified into two broad categories: a) the authors of particular GHQoL and OHQoL questionnaires; and b) experts with experience of using GHQoL and OHQoL questionnaires in preschool or early school aged child populations, including oral health research in particular. The experts were initially contacted by e-mail and further consultation was either done purely by e-mail or, in some cases, a further phone call was arranged. There were two purposes for contacting each group of experts: a) to acquire the full version of a questionnaire, and/or to clarify the wording of the instrument's recall period and/or school age related wording of questions, and to clarify the ability to change the recall period and wording according to the needs of the PT@3 study; b) to get the expert's view based on their previous experience of using different GHQoL/OHQoL instruments in preschoolers or early school aged children, to find out if they preferred particular instruments over others and to seek their advice on which questionnaires they would recommend for the PT@3 study.

Based on the information derived from the identified systematic and non-systematic reviews, expert opinions and when necessary using additional information searches (for example, for full texts of questionnaires), two tables, separately for GHQoL and OHQoL instruments, were created and populated with descriptive parameters (the age of child, respondent: parent or child, format of administering, recall period, number of domains and items) and columns with pros and cons. The main parameters included into the pros and cons were: the respondent burden (length of the questionnaire / time required to complete); whether / how widely it had been validated (worldwide and in the UK in particular); whether it was self- (child or parental proxy) or interviewer-administered; whether it had been developed specifically for preschool children / their parents or if the target age group was much wider; and whether there was a charge for using the instrument.

At a later stage two OHQoL questionnaires were dropped: one for being child self-report for ages five and over, and the other for being a proxy report for parents of children aged four years and over, with only one relevant previously published research paper found (involving young children), which reflected the original instrument's development. A table with more in-depth details on the

remaining OHQoL questionnaires was produced, containing information on the instrument's sensitivity and responsiveness to change, on the description of the studies where the instrument was used, and on the findings and issues uncovered in these studies.

The content of the tables and the results of the consultations with the experts were further discussed within the research team (the thesis author and her two PhD supervisors) and final decisions were made with regard to which instruments were to be used in the PT@3 trial.

4.4 Results – Review of general health-related quality of life instruments

A number of systematic and non-systematic reviews of GHQoL instruments were identified (Schmidt et al. 2001, Matza et al. 2004, Rajmil et al. 2004, Griebsch et al. 2005, King et al. 2005, Ravens-Sieberer et al. 2006, Solans et al. 2008, Hullmann et al. 2011, Petersen-Ewert et al. 2011, Kromm et al. 2012, Payakachat et al. 2012), the information on the GHQoL instruments contained within them was examined, and the questionnaires aimed at preschool populations were selected.

At the next stage, the following experts in the GHQoL area were consulted: Dr William Furlong, one of the authors of the Health Utilities Index (HUI); Dr Saroj Saigal, the author of Health Status Classification System Preschool (HSCS-PS) questionnaire; Mapi Research Trust, in relation to the Paediatric Quality of Life Inventory Generic Core Scale (PedsQL) and PedsQL Oral Health scale for toddlers; Dr Katherine Stevens, the author of the Child Health Utility 9 Dimensions (CHU9D); and Dr Lyndie Foster Page, in relation to using the CHU9D in dental health research. Further details are show in Appendix 10.

The information from the identified reviews was combined with the information received via personal communications with the experts and with the results of additional searches (e.g. for full text of the questionnaires). The questionnaires' descriptive parameters are presented in Table 4.1, whereas Appendix 12 also contains pros and cons (respondent burden, questionnaire validation, mode of

administration, whether it was developed specifically for preschool children / their parents), which were used in the decision-making process.

Eleven instruments used in preschool populations were identified. The majority of the questionnaires (eight, 73%) were developed specifically for preschool children (and sometimes included younger child ages, from babies onwards) and/or their parents/guardian. Two questionnaires were applicable to a vast range of ages up to older teenagers: Functional Status II(R) (FS II-R) can be used in children aged from zero to 16 years, and Quality of Well-Being Scale (QWB) can be used in four- to 18-year-olds. One questionnaire was designed to be used in preschoolers and younger school children (aged three to eight years) - TedQL.2.

The largest proportion of the instruments were developed in the USA – five out of the eleven (45%): Paediatric Quality of Life Inventory (PedsQL) Core, Infant Toddler Quality of Life Questionnaire (ITQOL), Child Health Status Questionnaire, FS II-R and QWB. Three (27%) were developed in the UK: Child Health Utility 9 Dimensions (CHU9D), Warwick Child Health and Morbidity Profile (WCHMP) and TedQL.2. And one in each of the following three countries: Kiddy-KINDL was developed in Germany, TNO-AZL Questionnaire for Preschool Children's Health-Related Quality of Life (TAPQOL) – in the Netherlands, and Health Status Classification System Preschool (HSCS-PS) – in Canada.

Four questionnaires were interview-administered (WCHMP, TedQL.2, FS II-R and QWB) and, hence, did not match our criterion of being a self-administered parental questionnaire. Of the remainder, two self-administered parental questionnaires were developed in a non-English speaking country and were not validated in the UK (Kiddy-KINDL (Harstick-Koll et al. 2009) and TAPQOL (Fekkes et al. 2000)).

Of the self-administered parental questionnaires that were developed in an English-speaking country, four were non-preference based: Child Health Status Questionnaire, ITQOL, HSCS-PS, and PedsQL Core (toddler version). The drawbacks of the first three of these questionnaires are briefly described below. The Child Health Status Questionnaire, was developed back in 1979 (Eisen et al.

1979) and was only used once since (Diaz et al. 1986). The ITQOL (Klassen et al. 2003) is long, which would cause a substantial burden on the respondent. The short-form contains 47-items, while the full-length version consists of 97 items. It was challenging to source a full sample questionnaire, but some of the wording seemed to be too infant-oriented (e.g. “nursing”, “rolling over”, “discomfort due to gas / teething”). In turn, the HSCS-PS was developed specifically to be used in the preschool aged populations (Saigal et al. 2005), however it is six pages long, which would cause a substantial respondent burden. In contrast, the PedsQL toddler parental proxy version is brief, practical and multidimensional (Varni 2020), and showed good psychometric performance in a UK toddler population (Buck 2012). The PedsQL measurement model, with its modular approach to measuring HRQoL, is long-established and widely used (PedsQL Website 2020).

Only two of the identified preschoolers’ questionnaires were preference-based, which meant they allowed calculation of utility and, in turn, QALY: the Quality of Well-Being Scale (QWB) and the Child Health Utility 9 Dimensions (CHU9D). As mentioned earlier, the QWB is an interviewer administered measure, which was developed in the USA. The CHU9D, on the other hand, has a self-administered parental questionnaire version and was developed in the UK.

The CHU9D was originally developed with children aged 7-11 years (Stevens 2011, Stevens 2012) and since then it has been validated in adolescent populations (11-17 years) ((Chen and Ratcliffe 2015) and Dr Katherine Stevens, personal communication, 2014). A preference-based scoring algorithm was developed using the UK adult general population employing the standard gamble method. The versions for younger children including a parental proxy for children of five years old and younger were being piloted at the time of this review.

The two GHQoL questionnaires chosen to be used in the PT@3 Study were the CHU9D (a preference-based instrument) and PedsQL Core for toddlers (a non-preference-based instrument). CHU9D was chosen as a GHQoL outcome measure for several reasons: it was developed in the UK using the UK adult general population for preference weighting (as opposed to the QWB, which was

developed in the USA), the CHU9D was self-administered (whereas the preschooler QWB was interviewer administered) and the author of the CHU9D, Dr Katherine Stevens, also identified the need to explore use of the instrument in preschool populations.

The CHU9D consists of nine domains: worried, sad, pain, tired, annoyed, nursery/school activities, sleep, daily routine, physical activities. There are five levels of response in each domain, rated from 1 (does not affect the child at all) to 5 points (affects very much). The possible utility range of the CHU9D questionnaire is from 0 (equivalent to being dead) to 1 (perfect health). The utility value can only be calculated for questionnaires with a full set of answers completed. The reference period is today / last night.

As the preschoolers' parental proxy version of the CHU9D had not yet been validated at the time when our research team had to make a decision in relation to which instruments were to be used in the PT@3 trial, it was decided to use two GHQoL questionnaires simultaneously: the CHU9D and the PedsQL (the two-to four-year-old parental proxy version). At the time when the majority of the work on the present GHQoL instrument review was conducted, there were no publications on the studies that used CHU9D in children under six years of age. They were work in progress at that time.

The PedsQL Generic Core Scale is a widely used non-preference-based instrument (PedsQL Website 2020), and the toddler parental proxy version has been used in the UK and performed well psychometrically in terms of internal consistency, reliability and acceptability (Buck 2012). The PedsQL Generic Core Scales are: brief (23 items), practical (it takes less than four minutes to complete), flexible (designed for use with community, school, and clinical paediatric populations), developmentally appropriate (with validated versions for different age groups), multidimensional (physical, emotional, social, school functioning), reliable, valid and responsive (Varni 2020).

PedsQL is a non-preference-based instrument, thus it provides a score, but not QALY. The reference period is past month. PedsQL Core Contains five domains: physical (8 items), emotional (5 items), social (5 items) and school/nursery

functioning (3 items). There are five response options for each item: never, almost never, sometimes, often and almost always. There are several summary scores within the measure: the psychosocial health summary score is the mean score on the emotional, social and school domains; the physical health summary score is the same as the physical functioning domain score; and the total scale score is the mean of all items in all domains (Varni 2017).

Table 4.1 General health-related quality of life instruments used in children aged 3-5 years

Instrument (Country of origin)	Age of child (years)	Respondent	Format of administering	Recall period	No. of domains (Items)
PedsQL, Paediatric Quality of Life Inventory (USA) Generic Core Scale	a) 2-4; b) 5-7	a) Parent; b) Parent, child	a-b) Questionnaire	a-b) Past 1 month; Also, there is “Acute version” of same q-res: past 7 days	a) 4 (21); b) 4 (23)
CHU9D for under 5-y.o., Child Health Utility 9D (UK)	(3)-5	Parent	Questionnaire	Today	9 + Question to rate child’s health
WCHMP, Warwick Child Health and Morbidity Profile (UK)	0-5	Parent	Interview	- in general; - in last year (depending on question)	10 (28)
Kiddy-KINDL (Germany)	3-6	Parent (Also a child version for 4-6 y.o.)	Questionnaire	Past week	6 (24) Plus a section of 22 additional questions
ITQOL, Infant Toddler Quality of Life Questionnaire (USA)	0-5	Parent	Questionnaire	Some scales ask about the past 4 weeks, the global health items asks about health "in general" and the global change items asks as compared to one year ago	47-item short-form (ITQOL-SF47); 97-item full-length version (ITQOL).
TAPQOL, TNO-AZL Questionnaire for Preschool Children's Health-Related Quality of Life (The Netherlands)	0.5-5	Parent	Questionnaire	Last 3 months	8 (43)
HSCS-PS, Health Status Classification System Preschool (Canada)	2.5-5	Parent	Questionnaire	Usually (usual health, usual ability) However, in one study a recall period of 1 week was used.	10 domains; plus 2 additional Qs (not part of the original Health Utility Index, that HSCS-PS is based on.)
TedQL.2 (UK)	3-8	Child	Interview	Usually	5 (23)
FS II(R), Functional Status II(R) (USA)	0-16	Parent	Interview	? (No information found)	8 (43 or 13)

Instrument (Country of origin)	Age of child (years)	Respondent	Format of administering	Recall period	No. of domains (Items)
Child health status questionnaire (USA)	a) 0-4; b) 5-13	Parent	Questionnaire	Past month / past 3 months (in different questions)	a) 3 (16) b) 5 (35)
QWB, Quality of Well-Being Scale (USA)	4-18	Parent	Interview	Past 6 days	3 (3 + 27 symptoms)

Notes: QALY – quality adjusted life year; YA – Yulia Anopa (the thesis author).

4.5 Results – Review of oral health-related quality of life instruments

Several systematic reviews of OHQoL instruments were found and examined in relation to the OHQoL instruments identified within them (Grange et al. 2007, Barbosa and Gaviao 2008a, Barbosa and Gaviao 2008b, Barbosa and Gaviao 2008c, Jankauskiene and Narbutaite 2010, Genderson et al. 2013, Gilchrist et al. 2014).

At the next stage, the following OHQoL experts were consulted: Dr Bhavna Pahel, the author of the Early Child Oral Health Impact Scale (ECOHIS); Dr Noelle Huntington, the author of the Paediatric Oral Health-Related Quality of Life (POQL) questionnaire; Dr Sara Filstrup, the author of the Michigan OHQoL Scale; Prof Georgios Tsakos, the author of the Scale of Oral Health Outcomes for 5-year-old children (SOHO-5) and an OHQoL expert; Dr Jenny Abanto, in relation to choosing between the SOHO-5 and ECOHIS; Prof Zoe Marshman, an OHQoL expert, in relation to the Caries Impacts and Experiences Questionnaire for Children (CARIES-QC) questionnaire and the use of other OHQoL and GHQoL instruments in child oral health research; and Mrs Amy Caldwell-Nichols, in relation to the questionnaires used in the FiCTION (Filling Children's Teeth: Indicated or Not?) trial. See Appendix 11 for further details.

Similar to what was carried out for GHQoL instruments, the information from the identified reviews was combined with the outcomes of personal communications with the experts and additional information searches.

Table 4.2 contains the OHQoL instruments that can be used in children three to five years old and includes both child self-report and parental proxy questionnaires. In addition, Appendix 13 contains pros and cons of these instruments.

The review identified six questionnaires that were used in children aged three to five years (inclusive). However, two of the questionnaires were excluded from further investigation. One of them was a child self-report for ages five and over (Caries Impacts and Experiences Questionnaire for Children (CARIES-QC)

(Gilchrist et al. 2018)), which was at the stage of being developed at the time of the review. The other excluded questionnaire, the Michigan OHQoL Scale (parental version), was a proxy report for parents of children aged four years and over, with only one previously published paper found (Filstrup et al. 2003), which reflected the original instrument's development and included children with a mean age of 4.2 years. This scale had undergone only limited testing in a clinical setting (Pahel et al. 2007) when the present review was conducted. Additionally, the Michigan OHQoL Scale has been mostly used in older children and adolescences, for example, (Munz et al. 2011, Hassan et al. 2014), rather than in preschool children.

Of the remaining questionnaires, one was developed specifically for use in preschool children aged two to five years (the Early Child Oral Health Impact Scale, ECOHIS (Pahel et al. 2007)), one was originally developed for five-year-olds (the Scale of Oral Health Outcomes for 5-year-old children, SOHO-5 (Tsakos et al. 2012, Abanto et al. 2013b)), and two instruments were designed for the whole childhood and adolescence cycle, with several separate age-appropriate versions (for example, for preschoolers, younger school children and teenagers): the Paediatric Oral Health-Related Quality of Life (POQL) (Huntington et al. 2011) and PedsQL – Oral Health Scale (PedsQL-OH) (Steele et al. 2009).

Further investigation was conducted for these four instruments. Three of them were developed in the USA: ECOHIS, PedsQL-OH and POQL, while SOHO-5 was developed in the UK. All four of them had a parental proxy-report self-administered questionnaire versions. Only SOHO-5 had a child-self report interviewer-administered version for a younger child (from five years old), whilst PedsQL-OH and POQL had child self-report questionnaire versions for older children (from eight years old).

Table 4.2 Oral health-related quality of life instruments used in children aged 3-5 years

Instrument (Country of origin)	Age of child (years)	Respondent	Format of administering	Recall period	No. of Items
ECOHIS – Early Child Oral Health Impact Scale (USA)	2-5	Parent	Questionnaire	*"child's entire life from birth until now"* A study by Li et al (2008) used *"previous 2 weeks"* (Li et al. 2008a, Li et al. 2008b)	13 (divided into 6 domains) Derived from Child Oral Health Quality of Life Questionnaire (COHQoL), which is aimed at older children/their parents (6 y.o. and over). 13 items taken from COHQoL's Parental Perceptions Questionnaire (PPQ) and Family Impact Scale (FIS).
POQL – Paediatric Oral Health-Related Quality of Life (USA)	a) 2-7; b) 8-14; c) teen (>14)	a) Parent; b-c) Parent and Child self-report	Questionnaire	Past 3 months	a) 6 + 7 "FIS" + Qs on parental dental health / dental visits; b) 10 + c) 17 +
Michigan OHQoL Scale – Child Version; Michigan OHQoL Scale – Parent/Guardian Version. (USA)	From 4 y.o.	a) Child; b) Parent GT, pers.comm.: Parent/ Guardian Version; 10 questions and can be used from 4 years old onwards (a shortened version was used with as young as 3 years of age).	Questionnaire	Not very clear: *"How much do you disagree/agree with the following?* *- My child has… / teeth are… "* Currently (?)	a) 9 b) 10
SOHO-5 – the Scale of Oral Health Outcomes for 5-year-old children (UK)	Developed for 5 y.o.	a) Parent; b) Child	a) Questionnaire b) Interview	Original – "ever"; GT suggested to use "12 months" for PT@3.	7
PedsQL – Oral Health scale (USA)	a) 2-4; b) 5-7; c) 8-12 d) 13-18	a) Parent; b-d) Parent, child	a-d) Questionnaire	Past 1 month	5
Caries Impacts and Experiences Questionnaire for Children (CARIES-QC) (UK)	5-16 y.o.	Child self-report	Questionnaire	Generally / Now (?)	17

Notes: GT – Georgios Tsakos; pers.comm. – personal communication; y.o. – years old.

Table 4.3 contains the information on the sensitivity and responsiveness to change and a short description of the populations of the studies where the four shortlisted instruments (ECOHIS, PedsQL-OH, POQL and SOHO-5) were used. Appendix 14 contains the description of the findings and issues uncovered in these studies. The two OHQoL instruments with most research papers identified were ECOHIS and SOHO-5.

As the purpose of the PT@3 Study was to compare the effectiveness of the fluoride varnish application plus treatment as usual with the effectiveness of treatment as usual alone, one of the main questionnaire properties of interest in this review was responsiveness to change. Namely, whether an instrument would be able to pick up changes in the child's OHQoL caused by new carious (decayed) teeth. The SOHO-5 questionnaire showed moderate longitudinal construct validity, good internal and external (anchor based) responsiveness and was proven to be responsive to change in a "before/after" study involving unspecified dental treatment (Abanto et al. 2013c). The authors of the same study recommended this instrument to be used in clinical trials.

The responsiveness to change of ECOHIS was tested in a convenience sample of 0-5-year-old children attending a hospital clinic for dental treatment (Li et al. 2008a). It was found that a large majority of parents reported low levels of impacts pre-treatment, despite reporting that their child had a dental problem requiring treatment. ECOHIS demonstrated some limited ability to respond to change on a group level, however, at an individual level, the instrument was somewhat imprecise. Moreover, the sensitivity was found to be "fairly good": with good sensitivity but a relatively high rate of false positive findings. The authors concluded that this instrument did not appear to be sufficiently precise to be used in a clinical setting (Li et al. 2008a).

Table 4.3 Comparison of the four shortlisted parental proxy OHQoL instruments

Instrument (Country where developed)	Age of child	Sensitivity / Responsiveness to change	Studies where the instrument was used?
SOHO-5 (UK) (Tsakos et al. 2012)	Under 5y.o., 5-6 y.o.	Before/after a dental "treatment" (not mentioned which exactly) (Abanto et al. 2013c) – showed moderate longitudinal construct validity… good internal and external (anchor based) responsiveness. …Is responsive to change and can be used in clinical trials.	1) UK: 269 child-parent pairs, 5 y.o. (Tsakos 2010) 2) Brazil: 193 child-parent pairs, 5-6 y.o; of those 154 pairs completed q-re post-treatment; children with/without caries and/or dental trauma (Abanto et al. 2013c). 3) Brazil: 193 child-parent pairs, 5-6 y.o. (with 159 test-retest sample) (Abanto et al. 2013a) 4) Brazil: 298 child-mother pairs, 5-6 y.o. (Abanto et al. 2013a) 5) Brazil: 335 child-parent pairs, 5-6 y.o.; children with/without caries and/or traumatic dental injuries (TDI) (Abanto et al. 2014a)
ECOHIS – Early Child Oral Health Impact Scale (USA) (Pahel et al. 2007)	2-5	Large majority of parents reported low levels of impacts pre-treatment, despite that they reported that their child had a dental problem requiring treatment. In this sample with low level of problems.. [it] has demonstrated some limited ability to respond to change. …Beyond these results, the sensitivity was fairly good (good sensitivity but a relatively high rate of false positive findings)… Although [it] has demonstrated some ability to be responsive to change on a group level, at an individual level, the instrument is rather imprecise…does not appear to be sufficiently precise to be used in a clinic setting (Li et al. 2008a) No statistically significant difference in mean B-ECOHIS scores over the 1-year period for all domains combined was observed (P = 0.40). However, a statistically significant difference in mean B-ECOHIS scores over the 1-year period was found for the domains 'child symptoms' (P = 0.03) and 'child psychology' (P = 0.02). The magnitude of the mean difference in mean B-ECOHIS scores was −0.24 (child symptoms) and −0.21 (child psychology). These domains reflected children's experience of pain, difficulty in sleeping and frustration/irritation because of oral problems	1) 295 parents of 5.y.o.chn.; 6 parents for test-retest (Pahel et al. 2007). 2) Convenience sample of 101 (94 with 2 sets of q-res) parents of 0-5y.o. chn.; pre dental treatment (restoration, pulpotomy, extraction, other) and 2 weeks after the treatment (ref.time was *"previous 2 weeks"*) (Li et al. 2008a) 3) 104 chn undergoing GA, 2-7 y.o., mean age 4.1 years (4 arm RCT: 16+30+30+28; Controls filled out ECOHIS while child was on waiting list for GA. In these cases GA was carried out after the study) (Klaassen et al. 2009) 4) Convenience sample of 50 child-parent pairs (31 before & after; 19 after only); chn undergoing GA (Klaassen et al. 2008) 5) 260 child-parent pairs, 2-5 y.o. chn with ECC, traumatic dental injuries and malocclusion (Abanto et al. 2011) 6) 826 6-7y.o. schoolchildren (cross-sectional) in deprived area; 587 parents returned q-re (Leal et al. 2012) 7) 302 chn 6-7 y.o. with cavitated primary molars. Three treatment groups. 277 parental q-res at baseline & 160 one year later (before/after treatments) (Leal et al. 2013) 8) Cross-sectional, 1,296 preschoolers/parents, 3-5 y.o.; 20%

Instrument (Country where developed)	Age of child	Sensitivity / Responsiveness to change	Studies where the instrument was used?
		(Leal et al. 2013) …the ECOHIS scores changed as expected with the gradient of parent's perceptions of treatment outcome, providing evidence of the measure's responsiveness. …Chinese version of the ECOHIS was sensitive to dental treatment for children aged 5 years or younger with ECC under GA. The measure also appeared to be responsive to the dental treatment for dental caries with respect to caregivers' global transition judgement with the outcome (Lee et al. 2011).	had severe ECC and 15% had ECC (Wong et al. 2011). 9) 111 chn, under 5 y.o., mean age 4.1 years. Two groups: with severe ECC, mean dmft = 7.44 (waiting for GA treatment) and caries-free. Reference period was *"1 month"* (Lee et al. 2010) [used PedsQL as well] 10) 398 parents of 12-mnth old chn (comm.-based intervention study); 94 parents of 0-5y.o. (hospital dental clinic). In 101 sub-sample of comm.group – second round of ECOHIS 2 weeks after the first (Li et al. 2008b). 11) 47 children 2-5y.o.and parents. Within a period of four-weeks, 20% of the participants repeated ECOHIS (Martins-Júnior et al. 2012). 12) 81 child-parent pairs, 0-5 y.o. with severe ECC, before/after GA. 3 rounds: pre-GA, 1 month post, and 3 months post (Pakdaman et al. 2014). 13) Consecutive sample of 32 (only!) child-parent pairs; 0-5 y.o. with ECC (mean age 4.5yr), undergoing GA. Before/after: 1 day before GA and 3 months after (Lee et al. 2011). 14) 138 chn, 5 y.o., internal migrants (China) / parents; mean dmft = 5.17; 52% with rampant caries – caries in >=2 smooth surfaces of maxillary incisors (Gao et al. 2011) 15) Cross-sectional, 1,215 child-parent pairs, 1-4 y.o.; looked at traumatic dental injuries, malocclusion and caries; 80% had not experienced dental caries (dmft=0); mean dmft = 0.72 (Abanto et al. 2014b) The Chinese, Farsi, Spanish and Lithuanian language versions have been also validated. [More ECOHIS publications exist, which were not reviewed due to time constraints.].

Instrument (Country where developed)	Age of child	Sensitivity / Responsiveness to change	Studies where the instrument was used?
POQL – Paediatric Oral Health-Related Quality of Life (USA) (Huntington et al. 2011)	2-7	At the 6-month recall ECC chn were rated by their parents as having significantly improved oral health and physical, mental, and social functioning comparing to the baseline. By contrast, improvements in emotional functioning were not seen… QoL was relatively constant for the ECC group between 6 and 12-m follow-up visits. Surgical dental intervention resulted in significant improvement on OHQoL in the first 6 months and remained improved after 12 months… The positive effects of a dental intervention for ECC chn are significant at the 6- and 12-months follow-ups, and enhance QoL in multiple domains …This study also supports the validity of items included into the parental version of the preschool POQL (Cunnion et al. 2010).	1) Diverse child populations in both school-based and clinic-based settings; data collected btw 2005-2008; 1,140 parental q-res analysed (Huntington et al. 2011) 2) 501 parents of 2-8 y.o. chn (315 caries-free & 186 with ECC); at baseline (before) and at 6 and 12 months after "dental treatment for ECC" (they also say "surgical dental intervention") (Cunnion et al. 2010) 3) 143 caregivers of young American Indian chn, mean age 2.1 years (range 0 – 7.25 y.o.); cross-sectional (Braun et al. 2013) No clinical dental assessment data for this study.
PedsQL-OH – Oral Health Scale (USA) (Steele et al. 2009)	a) 2-4; b) 5-7 c) 8-12 d) 13-18	No information found.	No studies were found that would have used PedsQL-OH specifically in preschool populations, only mixed-aged (e.g. 2 to 18 y.o.). 1) USA, English. Two samples: a) 126 families with chn aged 2-18 y. b) 34 families with chn 8-14 y.o. (Steele et al. 2009) 2) Iran, Persian: 1053 chn (8-18 y.o.) and 1026 parents. (Pakpour et al. 2011) 3) Brazil, Brazilian Portuguese: 208 chn (2-18 y.o.) and parents (Bendo et al. 2012).

Notes: YA – Yulia Anopa, ECC – early childhood caries, GA – general anaesthesia, TDI – traumatic dental injury, chn – children, y.o. – year-old.

The results of a study investigating different protocols for treating cavities in primary molars in 6-7-year-old children did not show overall improvements in the quality of life of children and their families one year after primary molars had been treated according to one of the three treatment protocols (Leal et al. 2013). No statistically significant difference in the total mean ECOHIS score over the one-year follow-up period was observed. The mean scores were low both at baseline and at follow-up, which averaged between “never” and “hardly ever” having problems of different types.

The Chinese version of ECOHIS was found to be responsive following an early childhood caries treatment under general anaesthesia in children under six years old (Lee et al. 2011). The ECOHIS scores changed as expected with the gradient of parent’s perceptions of treatment outcome.

With regards to the POQL questionnaire, a study aimed to compare changes in OHQoL of 2-8-year-old children between the two groups: children with severe early childhood caries (ECC) and children who were caries-free (Cunnion et al. 2010). The children with ECC received surgical dental intervention between baseline and follow-up. At the 6-month recall ECC children were rated by their parents as having significantly improved oral health and physical, mental, and social functioning comparing to the baseline. By contrast, improvements in emotional functioning were not seen. OHQoL was relatively constant for the ECC group between 6 and 12-m follow-up visits. Surgical dental intervention resulted in significant improvement on OHQoL in the first six months and remained improved after 12 months.

No information was found on the responsiveness to change of the PedsQL-OH add-on module.

At the final stages of decision-making with regard to which OHQoL instrument to use in the PT@3 Study, two measures were compared: ECOHIS and SOHO-5 (those used most frequently in published studies). An expert with substantial experience of using both instruments was contacted (Dr Jenny Abanto) to seek her opinion and preferences with regards to these two instruments. Dr Abanto felt that both instruments performed suitably well and was not able to say that

one of them was superior to the other. Another OHQoL expert was consulted in this regard - Prof Zoe Marshman, who recommended to use the SOHO-5 instrument. Taking in account the facts that the SOHO-5 questionnaire was shorter than the ECOHIS (7 items vs 13 items), SOHO-5 was developed in the UK (while ECOHIS was developed in the USA), and that the Community Oral Health section at the Dental School, University of Glasgow, team was previously involved in the original development and validation of SOHO-5 lead by the questionnaire's author, Prof Georgios Tsakos, it was chosen to be used in the PT@3 trial. Prof Tsakos was also supportive of the PT@3 Study and offered help if required.

The SOHO-5 consists of seven items: difficulty eating, difficulty speaking, difficulty playing, avoiding smiling (due to appearance), avoiding smiling (due to state of teeth), difficulty sleeping, self-confidence affected. There are six options for response: "not at all", "a little", "moderate", "a lot", "a great deal", and "don't know". The possible range of the total SOHO-5 score is 0 to 28. The lower the score, the better is the OHQoL. The reference period is the past 12 months.

A second OHQoL measure was selected to be used in the PT@3 trial. The PedsQL-OH (the two- to four-year-old parental proxy version), a short five-question add-on module, was added to the PedsQL Core Scale questionnaire – a non-preference-based GHQoL instrument selected earlier as one of the outcome measures for the PT@3 trial.

The authors of the PedsQL-OH suggested that this instrument might be used by researchers to screen for general oral health status in children in a cost-effective manner without the aid of a dental health professional. It is a brief five-item scale which may have potential use for identifying subgroups of children at risk for poor oral health at the population health level (Steele et al. 2009). A study investigating the reliability and validity of the Iranian (Persian) version of the PedsQL-OH concluded that it could be used in conjunction with the PedsQL Core to reliably and validly assess children's oral-health-related quality of life at the population level (Pakpour et al. 2011).

The PedsQL-OH is composed of five items and has two parallel instruments for child self-report and parent proxy-report. Child and adolescent self-report includes ages 5–7, 8–12, and 13–18 years. Parent proxy-report includes ages 2–4 (toddler), 5–7 (young child), 8–12 (child), and 13–18 (adolescent), and assesses parent's perceptions of their child's oral health. The items for each of the forms are essentially identical, differing in developmentally appropriate language, or first or third person tense (Bendo et al. 2012).

The PedsQL-OH contains five items: tooth pain, tooth pain when eating / drinking, teeth dark in colour, gum pain, blood on teeth after brushing. The response scale is the same five levels of response as for the PedsQL Core: from "never" (0 points) to "almost always" (4 points). Raw scores are converted to reversed scale scores (from 0 to 100) the same way as was described for the PedsQL Core score previously. The higher the 0-100 scale score, the better is the OHQoL. The reference period is the same as for the PedsQL Core: past month.

4.6 Discussion

The aims of the present review were: a) to identify, assess and provide descriptive characteristics of the existing GHQoL and OHQoL questionnaires that were developed for three- to five-year old children; b) to produce descriptive tables comparing the identified GHQoL and OHQoL instruments, respectively; and, finally, c) to provide recommendations on which GHQoL and OHQoL instruments would be best to be used in the PT@3 trial.

Inclusion of a range of HRQoL measures is recommended when conducting economic evaluations of clinical trials, on the grounds that they perform different tasks: a generic non-preference-based measure, a disease-specific measure and a preference-based measure (Drummond 2001, Raat et al. 2006). However, concerns about the measurement burden to the respondent should also be taken into account (Drummond 2001). Consequently, one of the objectives of this review was to identify one of each type of GHQoL (preference-based and non-preference-based) and OHQoL ("disease"-specific) measures to be used in the PT@3 Study. These measures had to be brief, in order not to overburden the respondents.

The review identified eleven GHQoL and six OHQoL questionnaires that were used in children aged three to five years (inclusive). The main target were parental proxy questionnaires on the child's GHQoL and OHQoL that could be self-administered by the parent/guardian of the child. Of the six GHQoL self-administered parental questionnaires that were developed in an English-speaking country, four were non-preference based and two were preference-based (which allows one to calculate QALY, and thus such instruments can be used in a cost-utility analysis).

The current review identified one previous systematic review of the GHQoL instruments used specifically in 0-5-year-old children (Grange et al. 2007) (the timeframe of their search was from January 1980 to January 2006). In addition, within the last two years, two more relevant papers were published: a non-systematic overview of GHQoL and some of the disease-specific instruments used in children under five years of age (Germain et al. 2019), and a study aimed at item generation for a new proxy health-related quality of life measure in very young children (Verstraete et al. 2020b), which contained a systematic review of GHQoL measures for children under seven years of age. Grange and colleagues (Grange et al. 2007) identified 16 measures used in children aged under 5 years of age, however, not all of them were included into the present review, as some of them were either aimed at children under the age of three years or were purely health status rather than GHQoL measures. The other two reviews (Germain et al. 2019, Verstraete et al. 2020b) did not identify any other relevant instruments, used in generally healthy 3-5-year-old populations, that would have been missed from the present review, apart from two instruments aimed at children with chronic conditions (DISABKIDS (Simeoni et al. 2007) and DISABKIDS Smiley Questionnaire (Chaplin et al. 2008)). This validates the results of the current non-systematic review.

A recent systematic review identified a wide range of paediatric OHQoL and GHQoL instruments used in oral health research among children and adolescents (Hettiarachchi et al. 2019). Five GHQoL instruments used among children and adolescents in oral health research were identified from that review: the Child Health Questionnaire, Infant and Toddler Child Quality of Life Questionnaire, PedsQL Generic Core Scale, CHU9D and EuroQoL-5D youth (EQ-5D–Y). Out of

those, only two, the CHU9D and EQ-5D–Y (with the targeted age range of 4–15 years old), were preference-based. The reason why the present review did not identify the EQ-5D-Y as one of the instruments used in 3-5-year-old children was that at the time when this review was conducted the EQ-5D-Y had only been validated in children over six years of age (Verstraete et al. 2020a).

The two GHQoL questionnaires chosen to be used in the PT@3 Study were the CHU9D (a preference-based instrument) and PedsQL Core for toddlers (a non-preference-based instrument). To date, the CHU9D is the only preference-based instrument where the descriptive system has been designed from its original inception with children and adolescents (Stevens 2009, Chen and Ratcliffe 2015) and it has been used in over 180 studies to date (in child and adolescent populations of various ages) (Hill et al. 2019).

Foster Page and colleagues investigated whether the CHU9D measure can be useful in child oral health research (Foster Page et al. 2014, Foster Page et al. 2015). One of their studies showed that 6-9-year-old children with no apparent caries (dental decay) had a higher mean CHU9D score than those with caries, indicating better GHQoL (Foster Page et al. 2014). However, this difference was not statistically significant. Their other study aimed to determine whether the CHU9D was responsive to the changing components of the dmfs+DMFS index score (a dental effectiveness score, which is the number of decayed, missing due to decay, and filled tooth surfaces in both the deciduous and permanent dentition) in children receiving dental care over a one year period (Foster Page et al. 2015). The results of that study indicated that no statistically significant relationships were found between caries status and the CHU9D score and the instrument was found to be unresponsive to the changing components of dental caries experience in 6-9-year-olds. However, children with decayed surfaces or those missing due to caries had lower CHU9D (indicating poorer GHQoL) scores than those with no decayed or missing surfaces, at both baseline and follow-up. Children with restored (filled) surfaces had higher CHU9D scores, indicating better GHQoL. The results of the study showed that the CHU9D might not be sensitive enough to be used as an outcome measure in economic evaluation in the area of paediatric dentistry, and it was found to be insufficiently responsive

to changes in caries experience or in the individual components of the dmfs+DMFS index (Foster Page et al. 2015).

The selected parental proxy preschool version of the CHU9D included the same domains and the same level of answers as the originally developed parental questionnaire (for 7-11-year-olds), but the wording of the questions was slightly different, with some explanations for the parents of preschool children added. The wording related to "schoolwork/homework" had to be further amended in consultation with the CHU9D author, Dr Katherine Stevens. An example of the questionnaire pack that was used in the PT@3 Study is shown in Appendix 15.

At the time when the majority of the work on the present GHQoL instrument review was conducted, there were no publications on studies that used CHU9D in children under six years of age. It was therefore decided to use the PedsQL (the two- to four-year-old parental proxy version) alongside the CHU9D. A previously conducted study in 5-6-year-old children used the same pair of GHQoL measures, albeit interviewer-administered child-report versions were used for both (Frew et al. 2015). The PedsQL family of long established GHQoL scales are brief and have good reliability and validity in both sick and healthy populations (Varni et al. 2007, PedsQL Website 2020, Varni 2020). The PedsQL is often chosen as a "gold standard" comparator as this is a widely used GHQoL instrument (Canaway and Frew 2013, Frew et al. 2015). The PedsQL toddler parental proxy version has been used in the UK and showed good psychometrical properties: internal consistency, reliability and acceptability (Buck 2012).

Our review identified six OHQoL instruments that were used in 3-5-year-old child populations. Of these, the ECOHIS parental proxy questionnaire was developed specifically for the use in preschool children aged two to five years, the SOHO-5 (with its child self-report and parental proxy-report versions (Tsakos et al. 2012, Abanto et al. 2013a)) was originally developed for five-year-olds, the Michigan OHQoL questionnaire was developed for ages four years and above, and two instruments were designed for the whole childhood and adolescence cycle, with several separate age-appropriate versions: the POQL and PedsQL-OH.

An earlier mentioned systematic review of paediatric OHQoL and GHQoL instruments used in oral health research among children and adolescents (Hettiarachchi et al. 2019), identified the same five OHQoL instruments that have been used in 3-5-year-olds, as were identified in the present review (ECOHIS, Michigan OHQoL Scale, PedsQL-OH, POQL and SOHO-5). In addition, the present review identified one more questionnaire that was not included into the Hettiarachchi and colleagues' paper: the CARIES-QC measure that was being developed at the time of this review and it was subsequently published in 2018.

Another recent systematic review with standardized comparison of available OHQoL instruments (Zaror et al. 2019) identified five questionnaires that were developed especially for children under six years of age. Three were included in the current review: the ECOHIS, Michigan OHQoL and SOHO-5, and a further two questionnaires were described: the Dental Discomfort Questionnaire (DDQ) (Versloot et al. 2004) and the Oral Health-related Early Childhood Quality of Life (OH-ECQOL, available only in one language - Hindi) (Mathur et al. 2014). The DDQ is an instrument that was developed specifically to identify toothache related behaviours in young children and includes two dimensions, namely occurrence of toothache and behaviour-associated discomfort (Versloot et al. 2004). It is not a full-range multi-dimensional OHQoL instrument.

Zaror and colleagues (2019) also identified four instruments designed for the whole childhood and adolescence cycle. Among them were the PedsQL-OH and POQL. The other two instruments in this group were the Family Impact Scale (FIS) (Locker et al. 2002) and the Parental-Caregiver Perceptions Questionnaire (P-CPQ) (Jokovic et al. 2003) – both are a part of the Child Oral Health Quality of Life Questionnaire (COHQoL) family of instruments (Jokovic et al. 2003). The review authors indicated that the applicable child age range for both the FIS and P-CPQ was 2-14 years. However, in the original P-CPQ development paper, the youngest children were six years old (Jokovic et al. 2003). Moreover, the wording of some of the questions in P-CPQ was deemed not to be relevant or appropriate for preschoolers (e.g. "missed school"; "attention at school"; "read out aloud"; "activities such as sport, clubs, drama, music, school trips"; "worried that he/she is (not)… as other people"). In turn, the FIS assesses the impact of the child's oral health state on the parents and the whole family and

covers such domains as parental/family activity, parental emotions, and family conflict (Locker et al. 2002). As such, the FIS does not assess the child's OHQoL.

In addition, Zaror and colleagues (Zaror et al. 2019) evaluated each instrument applying the Evaluating Measures of Patient-Reported Outcomes (EMPRO) tool. Out of the five instruments designed for preschoolers, the Early Childhood Oral Health Impact Scale (ECOHIS) obtained the highest overall EMPRO score (82.2; the possible range was 0–100, worst to best). The SOHO-5 overall EMPRO score was 53.1, while the scores for Michigan OHQoL, POQL and PedsQL-OH were 30.4, 69.0 and 45.8, respectively. EMPRO scores were considered reasonably acceptable if they reached at least 50 points (half of the 100 maximum theoretical points) (Zaror et al. 2019). Furthermore, SOHO-5, scored 100 points (the highest possible score) for responsiveness, however, the authors recommended more research on its reliability and interpretability. ECOHIS was the only questionnaire that had been culturally adapted to 14 languages or countries (Zaror et al. 2019), which may explain the fact that this instrument was used substantially more often than the other instruments, according to the present review.

The results of the two abovementioned systematic reviews (Hettiarachchi et al. 2019, Zaror et al. 2019) validate the present non-systematic literature review and confirm that no important preschoolers' OHQoL instruments were missed.

Two OHQoL instruments were selected to be used in the PT@3 trial: SOHO-5 and PedsQL-OH (the two- to four-year-old parental proxy version). The PedsQL-OH, a short add-on module, was added to the PedsQL Core Scale questionnaire, which was selected earlier as a non-preference-based GHQoL instrument for the PT@3 trial.

The original English language version of the SOHO-5, which was developed in the UK, showed high levels of internal consistency reliability and construct validity: presence of clinically diagnosed active dental caries was significantly associated with worse OHQoL (Tsakos 2010). It was found that parents tended to underrate their children's oral impacts, as parental perceptions of their children's OHQoL were lower than their children's self-reports. However, these results

contradicted the results of a Brazilian study which found very good agreement for mother-child pairs and concluded that the mothers may be used as good proxies (Abanto et al. 2013a).

The Brazilian Portuguese version of the SOHO-5 was used in several studies in Brazil. The parental questionnaire showed moderate longitudinal construct validity and good internal and external (anchor based) responsiveness. The authors concluded that the instrument was responsive to change and could be used in clinical trials. Both child self-report and parental proxy versions presented satisfactory results, however, the child version performed better (Abanto et al. 2013c). Another Brazilian study demonstrated good construct and discriminant validity, and high test-retest reliability and reproducibility properties. The SOHO-5 was able to clearly discriminate between children with and without a history of dental caries (Abanto et al. 2013a). In both child- and parental versions, caries was associated with worse children's OHQoL, for the total score and all SOHO-5 items (Abanto et al. 2014a). A study that compared the parental and child versions of the SOHO-5 found very good agreement for mother-child pairs, with mothers reporting equivalent OHQoL for their children as the children themselves. The authors concluded that the mothers may be used as good proxies in case the children are unable to complete the SOHO-5 (Abanto et al. 2013a).

The main limitations of the present review are that it was not a systematic review, but rather it used a snowballing approach, and that it was narrative in nature. Notwithstanding this fact, the results of this review agreed with those of several recent GHQoL and OHQoL systematic reviews. One of the strengths of this review is that it combined both literature searches and expert opinions.

With regard to the limitations of the preschoolers' GHQoL and OHQoL instruments themselves, the present review has identified only two preference-based GHQoL instruments that were used in children under six years of age: one interviewer-administered (QWB), and the other parental self-administered (CHU9D). Even then, the CHU9D was originally developed with children aged 7-11 years, rather than with preschool children; while QWB is applicable to a wide age range from 4 to 18 years, that is, again, it is not preschooler specific. There

are no existing preference-based OHQoL measures for preschoolers. Further research and development of new preference-based measures suitable for preschoolers (or their parents/guardians as a proxy) are required.

4.7 Conclusion

The present review of GHQoL and OHQoL measures identified a range of existing questionnaires for use in preschool populations – both for parental proxy reporting and child self-reporting. Their strengths and limitations were considered in relation to applying them in the PT@3 Study (a preschoolers' oral health randomised controlled trial). Four instruments were selected to be used in the trial: the CHU9D, PedsQL Core, PedsQL-OH and SOHO-5. The results of the review can assist researchers and programme evaluators in understanding the differences between the included GHQoL and OHQoL measures and to help them in choosing the best-suited instrument(s) for their projects.

Chapter 5 Protecting Teeth at 3 Economic Evaluation Rationale and Methods

5.1 Introduction to Chapter 5

Chapter 5 presents the methods used in the economic evaluation (EE) of the Protecting Teeth at 3 (PT@3) randomised controlled trial. Section 5.1 is an introduction, which provides the rationale for the PT@3 trial as well as a broader scientific background. Section 5.2 contains the PT@3 trial description, aims, trial design and methods and data collection methods. Section 5.3 describes the PT@3 within-trial economic analysis methods. It covers the economic evaluation frameworks employed, costs and outcomes used, it provides a description of how missing data were handled, as well as describing in detail the methods for each type of the EE analyses used (cost-utility, cost-effectiveness, and cost-consequence analyses).

5.1.1 Rationale for Protecting Teeth at 3 (PT@3) Study

In response to persistent poor oral health in Scotland, in 2005 the Scottish Government set out its policy "An Action Plan for Improving Oral Health and Modernising Dental Services in Scotland" (Scottish Government 2005). The Action Plan's aim was to shift the balance of care towards a more preventive and anticipatory care approach rather than treatment by targeting the early years age group. This action plan also outlined the Scottish Government's target for the National Health Service (NHS) Health Boards, stating that 60 per cent of five-year-old children should be decay free by 2010.

As it was previously mentioned in Chapter 1, dental caries is chronic and progressive in nature. It affects very young children, but is a lifelong condition that continues across adolescence and adulthood, and into later life (Peres et al. 2019). Socio-economic background, health-related behaviour patterns in early life years, and previous disease experience play important roles in terms of oral health outcomes later in life (ICOHIRP 2015, Peres et al. 2019). Inequalities in dental caries are observed between different ethnic groups, children from rural and urban areas, and across different area-based socioeconomic circumstances (Conway et al. 2014). For example, children from some ethnic backgrounds can

have higher caries prevalence than their white contemporaries over and above socioeconomic circumstances (Conway et al. 2007). Another example is that children in remote and rural areas of Scotland appear to have better dental health and a higher proportion of filled teeth when compared with those living in cities (Levin et al. 2010).

Childsmile is a whole-Scotland oral health improvement programme for children, which started with pilots commencing in 2006. There are several components of Childsmile, which include: daily supervised toothbrushing (with 1,000ppm - 1,450ppm fluoride toothpaste) in nurseries and in the first two years of primary school in the more deprived areas; free toothpaste and toothbrush packs for home use; community-based dental health support workers; biannual applications of fluoride varnish (FV) in targeted nurseries and primary schools; and preventive care including FV and oral health advice within primary dental services (Macpherson et al. 2010, Macpherson et al. 2015, Macpherson et al. 2019a, Macpherson et al. 2019b, McMahon et al. 2020).

One part of the programme that is targeted at children at an increased risk of dental caries is a nursery- and school-based FV application scheme. Children in the most deprived areas in each NHS Health Board in Scotland are offered twice-yearly application of FV via the education setting. A Cochrane systematic review of FV application concluded that it reduced worsening of caries in the primary dentition with a prevention fraction of 37% (Marinho et al. 2013). Three small trials of FV in the nursery/kindergarten setting (Grodzka et al. 1982, Chu et al. 2002, Borutta et al. 2006) were identified prior to the commencement of the PT@3 trial. They all showed a marginal caries preventive effect of FV against different comparison groups, but none of them had been undertaken as part of a wider public health programme (McMahon et al. 2020).

Chapter 3 revealed the paucity of high-quality economic evaluations (EEs) in preschoolers' caries prevention (Anopa et al. 2020). Although the number of EE studies relating to oral health improvement interventions in preschoolers has been increasing in recent years, a number of key EE components were inadequately reported in a substantial proportion of the reviewed studies. There was wide variation in types of caries prevention interventions investigated, in

effectiveness measures used, in how costs and outcomes were reported, and in study perspective used. Only one study that employed CUA, using a preference-based outcome measure, was identified. This notable lack of use of preference-based health-related quality of life measures in the field of preschoolers' oral health likely reflects the challenges with conducting EE in this young age group, the availability of suitable preference-based measures, and also flags up the limitations with regards to the use of these studies for the purposes of decision making in dental healthcare.

The systematic review reported in Chapter 3 (Anopa et al. 2020) has identified only two studies on fluoride varnish (FV) that employed cost-effectiveness analysis (CEA). One was a randomised controlled trial-based evaluation conducted in UK National Health Service (NHS) general dental practices (O'Neill et al. 2017) and the other was a USA-based Markov modelling study on Medicaid-enrolled children receiving interventions during Well-child visits at a medical centre during primary care (Quinonez et al. 2006). The results of both studies indicated that the interventions were not cost saving. It must be noted, however, that the study by O'Neill and colleagues (2017) was published after the methodology for the PT@3 EE had been developed.

No searches revealed any EEs of caries prevention randomised controlled trials that had been conducted in nursery/kindergarten settings.

In Scotland, where the PT@3 trial was conducted, in the school year 2013/14, 68% of 5-year-olds had no obvious decay experience in their primary teeth (NDIP 2014). The severity of dental caries in the population was assessed using obvious decay experience index (d3mft). In 2013/14, the d3mft in 5-year-old children living in Scotland was 1.27 per child, while for children with caries, the mean number of teeth affected was 3.97 per child (NDIP 2014).

The 2014 National Dental Inspection Programme (NDIP) report showed a continuing link between area-based socio-economic deprivation and poor dental health among 5-year-old children in Scotland. The absolute inequality between the most deprived quintile and the least deprived quintile remained at 30% (similar to the previous three survey years), with 53% of children in the most

deprived quintile (Scottish Index of Multiple deprivation, Quintile 1 [SIMD 1]) showing no obvious decay experience, compared with 83% of children in the least deprived quintile (SIMD 5) (NDIP 2014). In addition, the national target set in 2010 (namely, 60% of all 5-year-old children to have no obvious decay experience) was still not been met in SIMD1 in the 2013/14 school year.

The universal nursery supervised toothbrushing component of Childsmile had been previously shown to be both effective and cost saving (Macpherson et al. 2013, Anopa et al. 2015). However, there had been no evaluation of the added benefit of the nursery-based twice-yearly FV application component of Childsmile (McMahon et al. 2020). The nursery-based PT@3 trial aimed to assess the effectiveness and cost-effectiveness of additional preventive twice-yearly FV application plus other Childsmile programme interventions as usual, compared to usual Childsmile interventions alone (treatment as usual) (McMahon et al. 2020).

5.2 The Protecting Teeth at 3 (PT@3) randomised controlled trial

5.2.1 PT@3 description

The Protecting Teeth at 3 Study (PT@3) was a two-year parallel group randomised controlled trial (RCT) with an objective to compare the effectiveness of fluoride varnish (FV) plus treatment as usual (TAU; all other components of Childsmile), with TAU only in preventing any worsening of obvious decay experience, over a two year period from the first year of nursery education (aged three-years old) to the first year at primary school (aged five-years-old) (McMahon et al. 2020).

Three-year-old children attending the ante-preschool year at nursery schools were randomised (1:1) to the intervention arm (FV plus TAU, abbreviated ‘FV’ group further in the text) or the control arm (receiving TAU only). Children in the intervention arm had Duraphat® fluoride varnish applied to the surfaces of the primary teeth and also continued to receive TAU: all other components of Childsmile. Children in the TAU arm received the same series of contacts, without the application of FV and continued with the TAU. Interventions were undertaken by Childsmile trained extended duty dental nurses at six-monthly

intervals. Participants received a baseline dental inspection in nursery at the age of 3 years old and an endpoint inspection in primary school (Primary 1) at the age of 5 years old by trained and calibrated examiners (Wright et al. 2015, McMahon et al. 2020).

Trial registration: EUDRACT: 2012-002287-26; ClinicalTrials.gov: NCT01674933. The full protocol for the PT@3 trial was published previously (Wright et al. 2015).

5.2.2 PT@3 overall trial aims, including economic evaluation aims

The overall objective of the PT@3 trial was to compare the effectiveness of FV (plus TAU), with TAU only in preventing any worsening of obvious decay experience, over a two year period from the first year of nursery education (aged three years) to the first year at primary school (aged five years) (McMahon et al. 2020).

The economic evaluation aim was to assess the cost-effectiveness of preventive FV in the context of the Childsmile programme. Namely, to estimate the cost-effectiveness of the FV (plus TAU) intervention compared with TAU only (control) in three ways:

1. To conduct a cost–utility analysis (CUA) comparing the costs and utilities of the two groups over a 24-months period.

2. To conduct a cost-effectiveness analysis (CEA) comparing costs and effects between groups (the effect was oral health improvement or worsening, as measured by the d3mft).

3. To conduct a cost-consequence analysis (CCA) detailing resource use alongside all trial outcomes/consequences.

5.2.3 PT@3 trial design and methods, including economic evaluation

5.2.3.1 Trial management

The PT@3 trial was coordinated from the Community Oral Health unit at the University of Glasgow Dental School by the trial management group. The group included those individuals responsible for the day-to-day management of the trial, such as the Chief Investigator, statistician, trial managers, research nurse, and data manager. The role of the group was to monitor all aspects of the conduct and progress of the trial, ensure that the protocol was adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The Robertson Centre for Biostatistics, University of Glasgow, a UK Clinical Research Collaboration Registered Clinical Trials Unit, held all the records for the main PT@3 Study and were responsible for data management.

The thesis author's involvement in the trial included design of the EE section of the trial protocol; design of the documents to be submitted to the Ethics Committee for approval before the main EE data collection commenced (covering such items as child general health/oral health-related quality of life questionnaires, the protocol for the main staff cost and child quality of life data collection); face-to-face participant recruitment in the nurseries; design of the staff cost questionnaire and providing training to the staff delivering PT@3 interventions on how to fill in the cost questionnaire; design of the parental questionnaire pack on their child's general health/oral health-related quality of life; distribution of these parental questionnaire packs to parents/guardians (face-to-face, postal and, at a later date, online); overseeing and personally contributing to the collation and database entry of the returned questionnaires, as well as sending reminders to non-responder parents/guardians; data collection (trial cost data, parental questionnaires) and data analyses.

5.2.3.2 Target population

Trial participants were three-year-old children attending their first year of education in nursery schools within the areas of four NHS Boards in Scotland (NHS Greater Glasgow and Clyde, NHS Fife, NHS Lothian, and NHS Tayside).

Consent was obtained from the parents or guardians of the children. The children were included whether or not they had pre-existing dental caries lesions but were excluded if they had: (a) contraindications for the FV, i.e. hypersensitivity to colophony and / or any other constituents; (b) a history of bronchial asthma requiring hospitalisation; (c) a history of allergic episodes requiring hospital admission, or; (d) showing signs of distress on the day of the baseline inspection or showing signs of verbal or non-verbal reluctance. Recruitment was carried out from December 2012 in the three cohorts in the academic years 2012/13, 2013/14, 2014/15 (McMahon et al. 2020).

5.2.3.3 Sample size

From a local study of three-year-olds, it was estimated that approximately 41% of 3-year-olds from deprived communities would experience new decay over the course of two years of follow-up (McMahon et al. 2010). A two-group x2 test with a two-sided significance level of 0.05 would have 90% power to detect the difference between a group 1 proportion of 0.41 and a group 2 proportion of 0.31 (an odds ratio of 1.55) when the sample size in each group is 483. We therefore needed a total of 966 evaluable subjects (McMahon et al. 2020).

5.2.3.4 Setting and location

The nurseries which were targeted in each NHS area were those just above the cut-off for inclusion in the fluoride varnish scheme within the main Childsmile programme, namely, the next most socially disadvantaged areas based on the Scottish Index of Multiple Deprivation (SIMD) of the home postcode of the children (Scottish Government 2012b, Scottish Government 2012c). For example, if in a particular NHS Board area the nurseries with the highest proportion of SIMD1 (the most deprived quintile) children had been already included into the main Childsmile FV programme, then the nurseries with the highest proportion of SIMD2 (the next deprived quintile) children would be invited to participate in the PT@3 trial - the ones, that had not already been participating in the Childsmile FV programme.

The children were followed up into the first year of primary school. The overall study was conducted in the four NHS Boards outlined above, but only NHS Fife,

NHS Lothian, and NHS Tayside participated in the EE segment of the trial. EE commenced later than the main PT@3 trial was launched, as soon as an opportunity to add a health economics component became available. The EE was based on a subset of the overall PT@3 trial, namely the children that were recruited into the study within 2014/15 academic year. By that time NHS Greater Glasgow and Clyde had completed their commitment to the study and did not recruit any new participants in 2014/15.

5.2.3.5 Comparators

The intervention arm: fluoride varnish applications (FVAs) plus treatment as usual (TAU). TAU was all other routine components of Childsmile. FVA was Duraphat® fluoride varnish (50mg/ml) applied to the tooth surfaces of the primary teeth at 6-monthly intervals, with a total maximum number of four FVAs over the two-year course of the study. The standard Childsmile programme protocol was used to apply the FV to all tooth surfaces (Childsmile 2019a).

The control arm: TAU – all other routine components of Childsmile, apart from FVAs in the nursery/school settings. These included some or all of the following, depending on each child's circumstances: universal daily supervised toothbrushing (with 1,000ppm fluoride toothpaste) in nursery/primary school; free toothpaste and toothbrush packs for home use; community-based dental health support workers contacts; and preventive care including FV and oral health advice within primary dental services (Macpherson et al. 2019b, McMahon et al. 2020). Chapter 1, Section 1.11, contains more details on the Childsmile programme.

Children in the TAU arm also received the same series of dental nurse contacts, as the children in the intervention arm, but without the application of varnish. They received a "mock" varnish application (applicator brushing the teeth with no fluoride varnish on it).

5.2.4 PT@3 data collection, including economic evaluation data

5.2.4.1 Study Schedule

The schedule of contacts with the participating children is summarised in Figure 5.1. At baseline a dental inspection and randomization was carried out. Treatment visits were at baseline, six months, 12 months, and 18 months. Before each treatment a brief oral check was performed, and if the child had a temporary condition such as cold sores, abrasions, or systemic illnesses, then the treatment was not carried out although they remained in the study. After 24 months of follow-up the study finished with an endpoint dental inspection in the first year of primary school (McMahon et al. 2020).

5.2.4.2 Dental inspections

Dental inspectors undertaking the examinations all had routine training and calibration using the protocols of the Scottish National Dental Inspection Programme (NDIP) (NDIP 2018). Caries was assessed at the dentinal level (d3).

5.2.4.3 Randomization

Eligible children were randomized to receive either fluoride FV plus TAU or TAU only in a 1:1 ratio. Randomization followed the baseline dental inspection and took place via a telephone call to the Interactive Voice Response System (IVRS) at the Robertson Centre for Biostatistics, University of Glasgow, a UKCRC Registered Clinical Trials Unit. Blocks of two and four were used for each nursery school separately (McMahon et al. 2020).

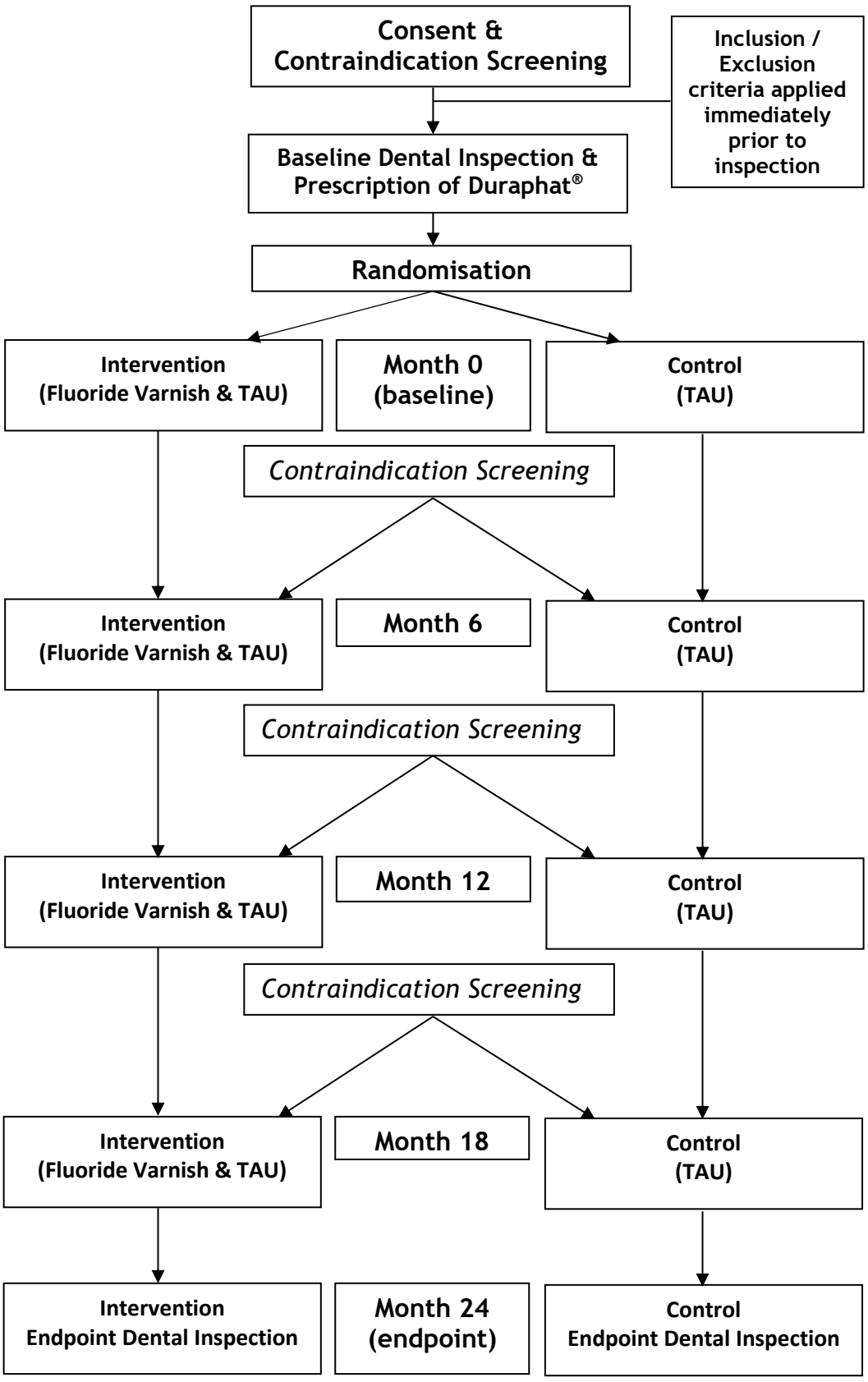

Figure 5.1 Trial visit schedule

Source (McMahon et al. 2020).

5.2.4.4 Allocation concealment and blinding

The treatment allocation was determined for each child by the IVRS and provided to the treatment teams at the time of the first treatment. The blocking was concealed to the treatment teams. The treatments were blind to the child (and therefore the parent/guardian) due to the "mock" application delivered to the TAU children and were also blind to the baseline and the final inspecting dental professionals (McMahon et al. 2020).

5.2.4.5 Dental outcomes and endpoints for effectiveness analysis

The primary outcome was dental caries as measured by d3mft. The primary endpoint was a worsening (i.e. a change that is greater than zero) in the primary outcome at 24 months, the end of the study. Secondary outcomes were d3mfs, a count of affected individual surfaces rather than the whole tooth, and the individual components that contribute to d3mft, namely dt (decayed teeth), mt (missing teeth), and ft (filled teeth). Secondary endpoints include a worsening of the secondary outcomes in a similar manner to the primary endpoint. Additional secondary endpoints included the absolute changes on a continuous scale, at 24 months of follow-up minus the d3mft at baseline, for all of the above endpoints (McMahon et al. 2020).

5.2.4.6 Economic evaluation data collection

The economic evaluation (EE) commenced later than the main PT@3 trial was launched, as soon as an opportunity to add a health economics component became available. The EE is based on the children that were recruited into the study within the 2014/15 academic year. The children attended 39 nursery schools in the NHS Fife, NHS Lothian and NHS Tayside areas.

The EE outcome measures were four different general health and oral health-related quality of life (GHQoL and OHQoL) measures collected at three points in time: the start of study (baseline), mid-study (in 1 year) and end of study (in 2 years). The GHQoL and OHQoL questionnaires were identified based on the review described in Chapter 4. The GHQoL measures were the Child Health Utility 9 Dimensions (CHU9D) and the Paediatric Quality of Life (PedsQL) Core,

while the OHQoL measures were the PedsQL Oral Health module (PedsQL-OH) and the Scale of Oral Health Outcomes for 5-year-old Children (SOHO-5) (Table 5.1). The recall period was “prior 12 months”.

Table 5.1 Economic evaluation outcome measures

Outcome measure	Baseline	12 mo.	24 mo.	Respondent / Source	Measuring what?	Economic evaluation framework
d3mft	X		X	PT@3 dental inspection	Clinical effectiveness	CEA / CCA
CHU9D (A preference-based measure, allowing to calculate utility and QALYs)	X	X	X	Parent/carer	GHQoL	CUA / CCA
PedsQL	X	X	X	Parent/carer	GHQoL	CCA
PedsQL-OH	X	X	X	Parent/carer	OHQoL	CCA
SOHO-5	X	X	X	Parent/carer	OHQoL	CCA

Notes: CHU9D – Child Health Utility 9 Dimensions, PedsQL – Paediatric Quality of Life Core, PedsQL-OH – PedsQL Oral Health module, SOHO-5 – Scale of Oral Health Outcomes for 5-year-old Children; d3mft - the number of decayed (into dentine), missing and filled teeth; QALY – quality adjusted life year; GHQoL – general health-related quality of life, OHQoL – oral health-related quality of life; CUA – cost-utility analysis, CEA – cost-effectiveness analysis; CCA – cost-consequence analysis; mo. – months.

5.2.4.7 General health and oral health-related quality of life measures

GHQoL and OHQoL data capture for the PT@3 trial

The review in Chapter 4 identified four instruments for measuring general health (a preference-based and a non-preference-based measure) and oral health-related quality of life, which were considered suitable for use in the EE of PT@3 trial. The instruments are summarised below.

The Child Health Utility 9D (CHU9D) is the only preference based GHQoL self-administered questionnaire developed in the UK specifically for children and their parents/guardians (Stevens 2009, Stevens 2011, Stevens 2012, Chen and Ratcliffe 2015) that was available at the time of the instrument selection. The

Paediatric Quality of Life (PedsQL) Core questionnaire is one of the most widely used non-preference-based instruments, which is often used as a "gold standard" comparator (Canaway and Frew 2013, Frew et al. 2015). The PedsQL Core has age-specific versions, including a toddler version for 2-4 year old children's parents/guardians (Varni 2019), which was used in this trial. The PedsQL Oral Health Scale (PedsQL-OH) add-on module was added to the PedsQL Core. The other oral health specific measure used was the Scale of Oral Health Outcomes for 5-year-old Children (SOHO-5) (Tsakos et al. 2012, Abanto et al. 2013a), which was developed in the UK with an active involvement of the University of Glasgow Dental School's Community Oral Health unit researchers. The SOHO-5 showed good overall psychometric properties, including excellent responsiveness (Tsakos 2010, Abanto et al. 2013c, Abanto et al. 2013b, Abanto et al. 2013a, Abanto et al. 2014a, Zaror et al. 2019) and was recommended for use in clinical trials (Abanto et al. 2013c). Further details of each of the questionnaires used in the PT@3 trial can be found in Chapter 4 (see Section 4.4 for GHQoL measures and Section 4.5 for OHQoL measures).

The authors of each questionnaire (or their representatives) were contacted by e-mail and/or video-call in order to receive permissions to use the questionnaires in the PT@3 EE. The thesis author had a video-call with Dr Katherine Stephens, the author of the CHU9D, in order to discuss the possibility of using the CHU9D questionnaire for our target group of three to five year old children, as by that time there was no published papers on the studies using it in children under six years of age. The necessity to change the wording in several questions, due to the children being of nursery age rather than school age, was also discussed and the changes were approved by the CHU9D author.

A draft version of the GHQoL and OHQoL questionnaire was piloted on a convenience sample of parents of 15 preschool and Primary 1 age children (together with the healthcare resource use costs questionnaire) in order to assess readability and comprehension of the questionnaires.

5.2.4.8 Questionnaire pack distribution

The questionnaires were distributed in a printed format either as a face-to-face survey, when a researcher visited the nursery, or, later on, using a postal distribution method (either to the parent/guardian's home address, or posted to the school for further distribution to the parents/guardians if their current home address was unknown). A proportion of the final round of the questionnaire pack distribution (at 24-months, the end of study) was done via an online method (Webropol, an online survey platform approved by the University of Glasgow, https://webropol.com/).

There was a series of reminders to non-responder parents/guardians: after one week post-distribution the non-responders received a text message, asking to complete and return the questionnaire; after two weeks post-distribution a second copy of the questionnaire pack was posted to the family's home address (or to the nursery address for further distribution); and after three weeks post-distribution the non-responders received a reminder phone call.

5.2.4.9 Participant healthcare resource use costs

Identification of participant healthcare resource use costs

The participant healthcare resource use costs questionnaire was developed in consultation with my PhD supervisors (Prof. Emma McIntosh – with health economics expertise, and Prof. Lorna Macpherson – with expertise in dentistry), through discussions with the trial managers, based on the questionnaires used by other colleagues at the Health Economics and Health Technology Assessment (HEHTA) research group at the University of Glasgow in previously conducted trials (Connolly et al. 2018) and on the questionnaires used in other EEs of child dental health trials elsewhere (Tickle et al. 2016, Chestnutt et al. 2017). A final draft version of the participant healthcare resource use costs questionnaire was piloted on a convenience sample of parents of 15 preschool and Primary 1 age children together with the quality of life questionnaire.

Measurement and valuation of healthcare resource use costs

Participant level resource use information was collected within-trial with the help of a resource use questionnaire, at three points in time: start of study (baseline), mid-study (at 12 months) and end of study (at 24 months). At each time point, the respondents were asked about their child's health care resource use within the preceding 12 months. Included were such items as number of general practitioner (GP) contacts, number of Accident and Emergency (A&E) attendances, number of visits to a family dentist, number of appointments with a dental hygienist, with a speech and language therapist, hospital inpatient stays (number of nights), hospital outpatient stay (number of attendances), and any other healthcare services used (free text) together with the number of times these services were used (see Appendix 15).

Medication use was also collected with the abovementioned resource use questionnaire (i.e. self-reported data). Medication costs were not included into the analysis; however, we investigated whether there was a difference in count between treatment arms in using or not using any medication (any medication used: yes/no).

Unit cost information was identified from routine sources such as the Personal Social Services Resource Unit (PSSRU) (Curtis and Burns 2017) and the NHS Reference Costs (NHS Improvement 2017a).

Table 5.2 Resource use unit costs, baseline year is 2016/17

Resource use item (per visit, unless otherwise stated)	**Unit cost**	**Source**
General Practitioner (GP)	£37	PSSRU 2017 p. 162. Per patient contact lasting 9.22 minutes.
Accident and Emergency (A&E) attendance	£192.33	NHS Reference costs 2016/17: Average of 'see and treat and convey' (by ambulance) (£248), 'see and treat or refer' (emergency care only) (£181) from Table 6, p. 9: 'Costs by currency for ambulance services between 2014/15 and 2016/17', and A&E attendance (£148); Table 2, p. 5: 'Unit costs by point of delivery, 2014/15 to 2016/17'.
Dentist	(127+186) / 2 = £156.50 £156.50 x 0.167 = £26.13	PSSRU 2017 p. 165-166. NHS dentist – Performer-only* £127 per hour of patient contact. NHS dentist – providing performer** £186 per hour of patient contact. Then the average of the two figures was taken. Assumption: 10 min (which is 0.167 of an hour) for each appointment.
Dental hygienist	1) £24.02 inflated from 2013/14 to 2016/17 is £25.00 2) Adding 55.1% earnings-to-expenses ratio = £38.77 3) £38.77 x 0.167 = £6.46 – cost of a 10 min appointment	British Dental Association (BDA) survey, 'Dental Care Professionals' Pay – Findings from the Dental Business Trends survey', 2013 (Edwards 2013), p.16, Appendix III, Average pay table for dental hygienists (£/hour): £24.02, Scotland figure. Inflated to 2016/17 level using HCHS annual pay indices – from PSSRU 2017 (p. 216) A 55.1% earnings to expenses ratio (Scotland 2016/17 data) added (NHS Digital 2018), following the Northern Ireland Caries Prevention In Practice (NIC-PIP) trial methodology (Tickle et al. 2016). Assumption: 10 min for each appointment. Health and Social Care Information Centre / NHS Digital: Dental Earnings and Expenses Estimates, 2016/17, p. 118, Tab 23.1 (bottom line, All / All)
Speech and language therapist	£94.91	NHS reference cost 2016/17 main schedule (Table 'Total Other Currencies'): A13C1 'Speech and Language Therapist, Child, One to One'
Hospital inpatient stay (per night)	£397.90	NHS reference cost 2016/17 main schedule, 'Total HRGs' tab; 'Regular day or night admissions' – Column Y. Average over all paediatric services (from record PC63A until PX57C).
Hospital outpatient stay	£198.20	NHS reference cost 2016/17 main schedule, Tab 'Total Outpatient Attendances', service code 420 – Paediatrics
Other resources filled in by	Various	Individually costed.

Resource use item (per visit, unless otherwise stated)	Unit cost	Source
parents (free text)		
Medications used (free text)	-	Costs were not assigned. We looked at whether any medication was used by each child (yes / no) to check if there was any difference between the groups. It was then considered that the use of medications was similar between the groups, and hence medications were not costed.

Notes: * A performer-only dentist is a qualified dentist who works in a provider-performer practice (e.g. a local dental practice). They are sometimes referred to as Associates.

** A providing-performer, which is a dentist who holds a General Dental Services contract and/or a Personal Dentist Services agreement with the NHS. They also act as a performer, delivering dental services themselves.

References: PSSRU 2017 (Curtis and Burns 2017); NHS Reference costs 2016/17 (NHS Improvement 2017a); NHS reference cost 2016/17 main schedule (NHS Improvement 2017b)

5.3 PT@3 within-trial economic analysis methods

Following UK's National Institute for Health and Care Excellence (NICE) public health economic evaluation guidelines a public sector perspective was taken, that of the UK's National Health Service (NHS). The time horizon was the duration of the PT@3 Study: two years. Following UK's public health economic evaluation guidelines a discount rate of 1.5% was employed (NICE 2012). The year of study completion, 2016/17, was used as the cost baseline year. All costs were valued in UK pounds sterling (£).

5.3.1 Economic evaluation frameworks employed

Three types of economic evaluation (EE) analyses were conducted: cost-utility analysis (CUA), cost-effectiveness analysis (CEA) and cost-consequences analysis (CCA). These types of EE were covered in more detail in Chapter 2, Section 2.5, hence, these are re-capped briefly below.

CUA is an EE in which the effects of different interventions are measured using utility units (e.g. QALYs). Alternative interventions are then compared in terms

of incremental cost per QALY (McIntosh and Luengo-Fernandez 2006). In the PT@3 trial, utilities and QALYs were estimated using a preference-based GHQoL instrument, the CHU9D, as described in detail in Section 5.2.4.7. Further details on the CUA methods used in the PT@3 Study are presented in Section 5.3.5.

CEA is an EE in which the effects of different interventions are measured using a single outcome, expressed as a natural unit (e.g. life years gained, reduction in d3mft, etc.). Alternative interventions are then compared in terms of incremental cost per unit of effect (e.g. incremental cost per unit reduction in d3mft) (McIntosh and Luengo-Fernandez 2006). In the PT@3 economic evaluation, CEA was conducted using the dental health effectiveness measure of d3mft (see Section 5.3.6 for further details).

CCA is a form of EE where disaggregated costs and a range of outcomes are presented to allow decision-makers to form their own opinion on relevance and relative importance to their decision making context (Drummond et al. 2005c). This is usually done using a descriptive table to present the effectiveness results (both primary and secondary outcomes) in a disaggregated format, together with the estimates of the mean costs with appropriate measures of dispersion associated with each intervention (Hunter and Shearer 2019). In the case of CCA, all impacts and costs are considered (even if the impacts cannot be costed) when deciding which interventions represent the best value. This type of analysis provides a “balance sheet” of outcomes that decision-makers can weigh up against the costs of an intervention (NICE 2013b).

In PT@3, the mean total costs and various outcome measures were compared. The outcome measures at 24 months were: d3mft, d3mft increment, OHQoL measures (namely, SOHO-5 and PedsQL-OH total scores and by item scores) and GHQoL measures (QALYs accumulated over the 24-month study period, utility index, the PedsQL total score and PedsQL domains, PedsQL and CHU9D scores by item). More details on the CEA methods used are presented in Section 5.3.7.

5.3.2 Costs

5.3.2.1 Identification, measurement and valuation of costs

A micro-costing (bottom-up) approach was used to estimate the costs. Resource use was identified through discussions with the trial managers and coordinators, the supervisors of this PhD project and other colleagues, based on previous EEs of child dental health trials (Tickle et al. 2016, Chestnutt et al. 2017) and by conducting observational visits to nurseries participating in the PT@3 trial. Resource use was then measured over the duration of the trial and were made up of the following data collection: (1) Intervention costs including staff labour, staff travel, and materials costs; (2) Participant healthcare (NHS) resource use, including service use and medications; and (3) Family costs (representing societal costs), which included time away from work / usual activities due to child's ill health, as shown in Table 5.3. Family costs were included in a sensitivity analysis.

Table 5.3 Economic evaluation resource use measures

Resource use category	Description of resource used	Unit of measure
Intervention costs		
	Dental nurses' time delivering PT@3	Hours / minutes
	Dental nurses' travel related to delivering PT@3	Mileage
	Disposable items used per child (by study arm: intervention / control)	£
	Reusable items used, cost per child (across both study arms)	£
Participant healthcare resource use		
	General Practitioner (GP)	No. of visits
	Accident and Emergency (A&E)	No. of visits
	Dentist	No. of visits
	Dental hygienist	No. of visits
	Speech and language therapist	No. of visits
	Hospital inpatient stay	No. of nights
	Hospital outpatient stay	No. of visits
	Other resources – filled in by parents/carers (free text)	No. of visits / Other (depending on the nature of a healthcare resource used)

	Medications used (free text)	Dichotomized: any medication used / not used (Yes / No)
Family		
	Time away from work /usual activities (due to child's ill health)	Days

5.3.2.2 Intervention costs

Staff costs questionnaire

Labour and staff travel costs related to PT@3 staff delivering interventions were collected during 2014/15 – 2016/17 (i.e. from the time the 2014/15 intake participants entered the trial to the time of their final interventions). Members of staff were asked to fill in a labour and staff travel costs form each time they visited a nursery (Appendix 16). The form contained such fields as names of the staff involved in a visit, mileage to and from the nursery, and the duration of the visit.

Development of the staff costs questionnaire

A staff costs questionnaire was designed and piloted in the NHS Greater Glasgow and Clyde area (an NHS Board that was participating in the PT@3 study prior to the main EE data collection year) in 27 nursery visits. Any feedback returned from the staff who filled in the pilot version of the costs questionnaire was considered and the draft amended accordingly, before finalising the version, which was later used in the PT@3 EE. In addition, the thesis author conducted five observational visits accompanying the staff delivering PT@3 interventions to nurseries (four in NHS Greater Glasgow and Clyde and one in NHS Fife). During these visits the composition of the intervention team and the timings of all relevant staff's actions were recorded, and the equipment used was documented. These visits were also used to ask the staff any relevant resource use questions.

An internal feasibility study was conducted in order to test the following parameters: a) logistics of the questionnaire distribution and return; b) the language and the layout of the questionnaire (whether it was clearly written and

easy to understand and follow); c) completeness of the returned questionnaires; and d) practicality of using the questionnaire in the PT@3 study.

Staff costs questionnaire – training for staff

The PT@3 trial staff delivering the interventions received face-to-face training from the thesis author. Any questions that the staff had in relation to the questionnaire were answered during these training sessions. The training was delivered in each of the three participating NHS Board areas, once within each year of the data collection (two academic years), prior to the commencement of that year's data collection.

Intervention costs valuation

Intervention costs were calculated for both the FV group and the TAU group (the cost of delivering a "mock" application). However, in the base-case scenario only the children in the FV group were assigned intervention costs, whereas the TAU group children were not. The cost of delivering a "mock" application to the TAU children was added in one of the sensitivity analyses (see Section 5.3.5.2).

NHS pay bands for each of the PT@3 staff members were requested from trial coordinators in the participating NHS Boards and mid-point salaries for each respective band range were used in the calculations. The Royal College of Nursing pay scales for NHS nursing staff in Scotland (hourly rate) was used (Royal College of Nursing 2016). The information on costs of disposable and reusable items used during FV visits were also requested from the trial coordinators. The cost components are illustrated further in the formulae below (Equation 5.1, A and B).

Equation 5.1 Intervention costs

Equation 5.1.A: $C_{intervention} = C_{labour} + C_{travel} + C_{disposables} + C_{reusables}$

Equation 5.1.B: $C_{labour} = \text{Staff's hourly rate} * \text{Duration of nursery visit (hh)}$

The cost of travel was calculated as mileage related to each nursery visit multiplied by the mileage rate. The approved mileage was 45p per mile (first 10,000 business miles in the tax year). The passenger payment was 5p per passenger per business mile for carrying fellow employees in a car or van (HM Revenue and Customs 2012). We used 47.5p per mile, based on an average number of PT@3 staff travelling together in one vehicle, which was 1.5 persons per car/van.

The cost of disposable items per child differed by study arm, with the main difference being the cost of the FV, the active ingredient. The average attributed cost of reusable items per child per visit, which was the same for children in both arms, was also calculated. In order to do this, the equivalent annual cost (EAC) formula was used (Equation 5.2):

Equation 5.2 Equivalent annual cost (EAC)

$$EAC = \frac{NPV}{A_{t,r}}, \text{ where } A_{t,r} = \frac{1 - \frac{1}{(1+r)^t}}{r}$$

where *NPV* is the net present value, *r* is the discount rate and *t* is the number of years (in this case, an average life span of three years was used).

The equivalent annual cost (EAC) of the reusable items used during the intervention visit was calculated with Equation 5.2. The net present value (NPV) of £532.49 (see Table 5.5) was used, the discount rate (r) was 1.5% and the number of years (t) was three years – an average life span. The resulting EAC was £182.85. It was assumed then that each reusable 'kit' was used every working day by the usual mainstream Childsmile programme, which equated to five working days a week, resulting in 240 working days per year and, which, in turn, equated to the number of times each kit was used over a course of a year. The cost per each use was calculated as: EAC / 240 = £182.85 / 240 = £0.76. A mean cost per child per visit was then calculated: the average number of children seen per PT@3 intervention visit was ten, hence, the reusables cost per child, per visit was £0.76 / 10 = £0.076, which was rounded up to £0.08.

The PT@3 intervention costs per child are detailed in Table 5.4 and Table 5.5. The disposable items cost was £2.32, reusable items cost was £0.08, staff travel: £1.78 and staff labour cost: £7.59.

Table 5.4 Disposable items used per child in the FV (intervention) group

Item	Cost (£)
Thin plastic tray	£0.60
Plastic dental mirror	£0.25
Plastic FV brush	£0.08
Cotton wool roll x 4	£0.02
Duraphat – fluoride varnish	£0.62
Gloves	£0.04
Hand gel	£0.01
Paper towel	£0.70
Total	£2.32

Note: The costs were provided by a PT@3 study coordinator.

Table 5.5 Reusable items used during the intervention visit

Item	Cost (£)	Notes
Beanbag	£89.98	The cost was provided by a PT@3 coordinator.
Clear plastic stack box (to hold all disposable FV materials)	£34.62	The cost was provided by a PT@3 coordinator.
Lockable container (black metal box with a lock)	£7.89	For Duraphat tubes storage. The cost was provided by a PT@3 coordinator.
Daray dental examination light on tripod	£400	Cost sources: http://www.daray.co.uk/shop/lighting/examination/x100-led-mobile-examination-light.html (£420) https://www.medisave.co.uk/daray-x100-led-examination-light-with-flexible-arm-mobile.html (£395)
Total	£532.49	
Total cost per child per visit (see calculations below)	£0.08	

Total intervention cost per child

In order to get a mean labour and staff travel cost per child in the FV group, the calculated sum of labour and travel costs per each visit was divided by the number of children that received an intervention (either a real FV application or a "mock" application) during that visit. Mean costs per child for disposable (depending on the number of successful visits each child received during the trial) and reusable items were then added on an individual participant's basis in

order to get the overall intervention cost per child. The total intervention cost per child was then calculated using Equation 5.1.A.

5.3.3 Outcomes

Effectiveness in the CUA was expressed in quality adjusted life years (QALYs). QALYs were estimated using the utility index values generated from the CHU9D questionnaire, as described in Section 5.2.4.7. The area-under-the-curve method was used to estimate QALYs over a 12-month period, following the trapezium rule assuming a linear change in utility between each assessment time point (Matthews et al. 1990, Brazier et al. 2016), in this case at 0-, 12- and 24-months.

The cost-effectiveness outcome was based on the d3mft effectiveness measure. The d3mft effectiveness data were analysed using a "difference in difference" approach. The "d3mft difference" was used as an outcome, which for each child in each study group was the difference between their d3mft at 24-months minus their d3mft at 0-months.

The following outcomes were used in the cost-consequence analysis (CCA): QALY, d3mft difference, OHQoL outcomes at 24-months (PedsQL-OH and SOHO-5 scores) and GHQoL outcomes at 24-months (CHU9D utility values, PedsQL total score and PedsQL scores by separate domains, as well as CHU9D and PedsQL individual item scores).

5.3.4 Handling missing data

The data were considered missing if participants were still in the study at each point in time (i.e. they had not withdrawn from the study) but did not have certain costs or utilities available in the study database.

Missing health and dental care resource use costs were treated differently, depending on the pattern of missingness in each returned parental questionnaire. If the questionnaire was not returned altogether (at any of the three distribution points) or a whole resource use section was left blank by the respondent, these resource use costs were considered to be missing. However, in the case where a respondent put some ineligible information in a resource use

field (such as a GP's contact telephone number instead of the number of contacts with a GP), it was assumed that the child did use that service and a mean number of contacts based on all available cases per each round of questionnaire distribution (at 0, 12 or 24 months) was assigned.

5.3.4.1 Mean imputations of baseline values

All remaining missing baseline (0-month) resource use and utility data were imputed using mean imputation. Each missing value of the baseline resource use items and utility data was filled in with the mean of all values observed at baseline (by item). This is the recommended method of dealing with missing baseline data (Faria et al. 2014). It ensures that the imputed values are independent of the treatment allocation.

5.3.4.2 Multiple imputations

Multiple imputation (MI) with chained equations was used to handle missing data on resource use costs and outcomes at the 12- and 24-months points. MI recognises the uncertainty associated with both the missing data and estimated parameters in the imputation model (Faria et al. 2014). The use of MI requires a less strong assumption regarding the missingness mechanism than the assumption needed to perform complete-case analysis (Paton et al. 2016).

The MI procedure includes three steps:

1) Imputation step: Regression models are used to predict plausible values for the missing observations from the observed values (Faria et al. 2014). Missing values in each dataset are drawn from the distribution of the missing data given in the observed data (Pedersen et al. 2017). This process is repeated m times, creating m imputed datasets. Generating multiple datasets reflects the uncertainty arising from imputation. It is suggested that the number of imputed datasets (m) should be similar to the percentage of incomplete cases (White et al. 2011).

2) Estimation step: Each dataset is analysed separately using a chosen analysis method to estimate the quantity of interest (e.g. costs and QALYs

in each treatment group). There is variability both within and between the imputed datasets because of the uncertainty related to missing values (Pedersen et al. 2017).

3) Pooling step: The estimates obtained from each imputed dataset are combined using Rubin's rules (Rubin 2004) to generate an overall mean estimate of the quantity of interest together with its standard error. Rubin's rules ensure that the standard error account for both the between- and within-imputation variations (Faria et al. 2014, Pedersen et al. 2017).

The predictive mean matching method for multiple imputation was used to account for the non-normality of the distribution of costs and utility scores. This method ensures that the imputations took only values from the data that were available in the original trial data (Paton et al. 2016). By applying predictive mean matching, predictions that lie outside the bounds of each variable were avoided (White et al. 2011).

The resource use costs were imputed at the total resource use cost level (i.e. all resource use items summed up by participant at each questionnaire round), and the missing CHU9D data were imputed at a utility score level. This was done to avoid convergence issues of imputation model when containing many variables. It was assumed that data were missing at random. Intervention and control groups were imputed separately (Faria et al. 2014). A total of 50 imputed data sets was generated to improve efficiency (Graham et al. 2007, White et al. 2011). To further inform the imputation model the following auxiliary variables were included: age, sex, level of deprivation (SIMD), caries at baseline, baseline utility, baseline parental time off work and baseline child time off nursery.

Cost data often have a heavily zero-inflated right skewed distribution (Glick et al. 2014), and as the PT@3 children were a generally healthy population, the predictive mean matching method on log-transformed costs was employed as recommended in this case (MacNeil Vroomen et al. 2016). A £1 constant was added to the raw cost data to avoid problems when transforming zero values (Glick et al. 2014) before the log-transformation. The distribution of utilities in

generally healthy populations is usually left skewed, with most children reporting high GHQoL (closer to 1) and smaller numbers in worse health states, therefore a similar manipulation was done with the utility values. First, a constant was introduced (1.1 minus the utility value), and then these resulting values were log-transformed. After imputation, both the cost and utility data were transformed back to the original scale for estimation (MacNeil Vroomen et al. 2016).

Following the use of MI, the uncertainty of the generated values was incorporated in the estimation of mean costs and utilities using a Rubin's rule (Rubin 2004, Paton et al. 2016). A visual inspection of the histograms of the non-imputed and combined imputed variables was conducted to confirm that both distributions were similar (Webb et al. 2019). The multiple-imputed datasets were then used to estimate the difference in QALYs and costs, and the incremental cost-effectiveness ratio (ICER). MI of missing values was conducted in Stata version 16.0 (StataCorp, College Station, TX, USA).

5.3.5 Cost-utility analysis

5.3.5.1 Cost-utility base-case analysis

The mean costs and QALYs for each group were presented using the method of recycled predictions (Glick et al. 2014). Incremental costs and QALYs, along with their corresponding robust standard errors, were reported from the results of generalised linear models.

Regression analyses of costs and QALYs

Differences in cost and QALYs between the intervention and control groups were estimated using generalised linear models (GLM) which offers a flexible framework to handle adjustment for baseline covariates when the distribution of the dependent variable is right skewed (Barber and Thompson 2004). GLMs have a variety of forms characterised by two features: a distribution function for the outcome data (in this case, costs and QALYs) and a link function, which describes the scale on which covariates in the model are related to the outcome (Barber and Thompson 2004).

Within GLM, the gamma distribution is often used to model continuous variables that are uniformly positive and have skewed distributions (such as cost and QALY data)(Barber and Thompson 2004, Moran et al. 2007, Skrepneka et al. 2012). In order to transform the left skewed QALY data into a right skewed and left bounded by zero QALY variable that would fit into a gamma distribution, the method of predicting decrements of QALYs was applied as suggested in a previous NIHR HTA report (Paton et al. 2016). Namely, QALY decrements were calculated as the difference between the maximum QALYs that could possibly be accrued within the time horizon of the analysis (24 months) and the actual QALYs gained. Identity link function was applied to costs (as it fitted better than a model with a log link), and log link was used for QALY decrements.

Costs and QALY decrements were adjusted for the following baseline covariates: treatment group, age, sex, SIMD, caries at baseline, baseline utility and baseline resource use cost. Regression analysis was conducted in Stata version 16.0 (StataCorp, College Station, TX, USA).

Probabilistic sensitivity analysis

A probabilistic sensitivity analysis was conducted by jointly bootstrapping the mean difference in cost and QALYs to produce 1,000 paired estimates. This allows accounting for the uncertainty due to sampling variation in the participant-level data (Webb et al. 2019). Non-parametric bootstrap with replacement was used. The draws were randomly selected, with replacement, from each treatment group. The total sample size of each bootstrap iteration was equal to the original trial's EE sample size (n=534). At the end of the process 1,000 resampled datasets were generated, each of which was equivalent to a repetition of the trial, and all of which had the same sample size as the original trial EE sample (Glick et al. 2014). Within each of the multiple "trials", a statistic of interest was calculated (mean cost, mean QALY, the difference in the means), and by doing it multiple times a distribution of the statistic of interest was generated. This distribution was then used to conduct non-parametric hypothesis testing (Glick et al. 2014).

The results of this non-parametric bootstrapping (the bootstrapped pairs of mean cost and QALYs) were then graphically presented on a cost-effectiveness plane. Cost-effectiveness acceptability curves (CEACs) were also constructed. The CEAC shows the probability of the PT@3 fluoride varnish intervention being cost-effective under a wide range of hypothetical cost per QALY thresholds (£0 - £100,000). In the UK, interventions are considered to be cost-effective if the cost per additional QALY gained is within the range of £20,000-£30,000 per QALY gained (NICE 2013a).

5.3.5.2 Cost-utility sensitivity analyses

Several one-way sensitivity analyses were designed *a priori* in order to assess the impact of uncertainty on the cost-effectiveness results. Exploration through sensitivity analyses strengthens the external validity and generalisability of the results. A description of each sensitivity analysis scenario is described in Table 5.6.

In Scenario SA1 intervention costs (related to the "mock" application) were added for TAU children. This scenario reflects the actual PT@3 trial logistics, when the PT@3 dental nurse teams did see the children from the control arm, but instead of the real fluoride varnish being applied to their teeth, their teeth were touched with an empty applicator (without an active ingredient). In the case of the control group children, the intervention cost would include the cost of labour, cost of travel to/from the nursery (labour and travel costs were the same per child as for the intervention group children by individual nursery visit), cost of disposables (without the fluoride varnish cost) and cost of reusables (same as for the intervention group children).

Scenario SA8 was added post-hoc, when outlier observations in relation to participant healthcare resource use were identified. These were the four children who had more than 45 Speech and Language Therapist contacts indicated at either the 12-months or 24-months data collection points, who consequently had substantially higher healthcare resource use costs than the rest of the sample. In Scenario SA8 these four observations were removed from the dataset.

Table 5.6 Sensitivity analyses scenarios investigated

Sensitivity analysis	Element	Variation for the sensitivity analysis
SA1	Costs	Intervention costs (related to the "mock" applications) were added for TAU children.
SA2	Costs	"Other" resource use costs added for both FV and TAU groups (i.e. the costs of the healthcare resources listed by the respondents in a free text field under "other" resources used)
SA3	Costs	Intervention costs 30% less than in the baseline scenario.
SA4	Costs	Intervention costs 30% greater than in the baseline scenario.
SA5	Discount rate	Use of a traditional 3.5% discount rate for costs and outcomes
SA6	Perspective / Costs	Cost of parental time off work (due to child's health issues) was added. This represents societal costs perspective.
SA7	Missing data	Available case analysis. Data assumed to be missing completely at random.
SA8	Outliers (participant healthcare resource use / cost)	Four outlier observations were removed from the dataset (those children who had more than 45 Speech and Language Therapist contacts indicated at either 12-mo. or 24-mo. data collection points).

5.3.5.3 Cost-utility subgroup analyses

Two types of subgroup analyses were planned *a priori*: a) by deprivation; and b) by presence/absence of caries at the baseline. However, it was not possible to meaningfully run either of them due to low numbers in the relevant subgroups within the EE sample.

5.3.6 Cost-effectiveness analysis

Cost-effectiveness analysis (CEA) was conducted using the dental health effectiveness measure of d3mft. The d3mft effectiveness data were analysed using a "difference in difference" approach. The "d3mft difference" was used as an outcome, which for each child in each study group was the difference between their d3mft at 24-months minus their d3mft at 0-months. A positive d3mft difference means worsening of the oral health state. The principle used to

calculate the ICER is shown in Table 5.7. Here, the difference in difference is [(e-c) - (f-d)].

Table 5.7 ICER for cost-effectiveness analysis on d3mft

	Total cost (mean)	d3mft at baseline (mean)	d3mft at end of study (mean)	Difference in d3mft	ICER
FV	a	c	e	(e-c)	(a-b) / ((e-c) - (f-d))
TAU	b	d	f	(f-d)	
Difference	(a-b)			(e-c) - (f-d)	

5.3.7 Cost-consequence analysis

The components of the cost-consequence analysis (CCA) are presented in Table 5.8. The mean values by group with the corresponding 95% confidence intervals (CI) were reported, as well as the mean difference between the groups with 95%CI. Total costs and various outcome measures were compared. The outcome measures at 24 months were: d3mft, d3mft increment, OHQoL measures (namely, SOHO-5 and PedsQL-OH total scores and by item scores) and GHQoL measures (QALYs accumulated over the 24-month study period, utility index, the PedsQL total score and PedsQL domains – physical, emotional, social, school and psychosocial, PedsQL and CHU9D scores by item).

Total costs and accumulated QALYs were analysed based on the multiple-imputed dataset, whereas d3mft, utility, OHQoL and GHQoL measures were analysed based on the available cases (i.e. the missing values were not imputed).

In addition, an exploratory comparative analysis of all GHQoL and OHQoL measures (CHU9D, PedsQL Core, PedsQL-OH and SOHO-5) by domain and by individual questionnaire item at 24-months (end of study) by study group was also conducted as a part of the CCA.

Table 5.8 Cost-consequence analysis components

Costs / Outcomes
Costs (MI dataset)
Total cost
Outcomes:
QALY
Dental health (ACA)
d3mft at 0 mo.
d3mft at 24 mo.
d3mft difference (d3mft at 24 mo. minus d3mft at 0 mo.)
OHQoL outcomes at 24 mo. (ACA)
PedsQL-OH score
SOHO-5 score
PedsQL-OH scores by item
SOHO-5 scores by item
GHQoL outcomes at 24 mo. (ACA)
Utility (CHU9D)
PedsQL - Total score
PedsQL - Physical domain score
PedsQL - Emotional domain score
PedsQL - Social domain score
PedsQL - School domain score
PedsQL - Psycho-social domain
CHU9D scores by item
PedsQL scores by item

5.4 Summary

There is a paucity of high-quality economic evaluations (EEs) in preschoolers' caries prevention. The PT@3 Study is the first nursery-based fluoride varnish (FV) effectiveness trial with an incorporated EE component, which assessed the preventive effect of FV in the context of the Childsmile programme.

This chapter firstly provided the rationale for the PT@3 Study, and the broader scientific background to the trial. Then an overview of the PT@3 randomised controlled trial was presented (with its overall aims, design and data collection methods). Finally, the within-trial EE methods used in the PT@3 (including the EE frameworks used, the details on how cost and QALY data were treated, the methods used to handle missing data, the description of the CUA, CEA and CCA analyses used) were described. The next chapter reports the results of the PT@3 economic evaluation.

Chapter 6 Protecting Teeth @ 3 Economic Evaluation Results

6.1 Introduction to Chapter 6

Following from Chapter 5, which presented the methods that were used in the economic evaluation (EE) of the PT@3 Study, Chapter 6 presents the results of this EE. The sections follow the same order as the sections in Chapter 5. First, the baseline characteristics of the EE sample are presented, followed by parental questionnaire response rate, missing data, and costs and outcomes results. Further on, the results of a series of analyses are presented in Sections 6.8-6.10: cost-utility analysis (CUA), cost-effectiveness analysis (CEA) and cost-consequence analysis (CCA). These are followed by the discussion of the results, the strengths and limitations of this study, and the conclusions.

6.2 Baseline characteristics of the study population

The baseline characteristics of the EE sample (N=534) are described in Table 6.1. The mean age of the children was 3.53 years (standard deviation, SD=0.24) and was balanced between the treatment groups (FV 3.52, TAU 3.54). The proportion of females was similar in both groups, with 136 (51%) in the FV group and 145 (54%) in the TAU group. The distribution of the categories of SIMD was similar in both groups. The proportions of children with pre-existing caries were identical in the FV group (n=37, 14%) and in the TAU group (n=38, 14%).

Three Health Board areas and 39 nursery schools participated in the EE component of the trial: 21 nurseries, 297 children in NHS Lothian; 9 nurseries, 121 children in NHS Fife; and 9 nurseries, 116 children in NHS Tayside. The breakdown by nursery and intervention group is shown in Table 6.2.

Table 6.1 Baseline characteristics of the economic evaluation sample

Variable	FV (n = 265)		TAU (n = 269)		Total (N = 534)	
	Mean	**(SD)**	**Mean**	**(SD)**	**Mean**	**(SD)**
Age	3.52	(0.24)	3.54	(0.24)	3.53	(0.24)
	n	**(%)**	**n**	**(%)**	**N**	**(%)**
Sex						
Female	136	(51%)	145	(54%)	281	(53%)
Male	129	(49%)	124	(46%)	253	(47%)
SIMD						
1	24	(9%)	16	(6%)	40	(7%)
2	89	(34%)	101	(38%)	190	(36%)
3	69	(26%)	80	(30%)	149	(28%)
4	52	(20%)	41	(15%)	93	(17%)
5	30	(11%)	31	(12%)	61	(11%)
Unknown	1	(0%)	0	(0%)	1	(0%)
Caries at baseline *	**n = 264***		**n = 267***		**n = 531***	
Yes	37	(14%)	38	(14%)	75	(14%)
No	227	(86%)	229	(86%)	456	(86%)

Notes: FV – Fluoride Varnish treatment group; TAU – Treatment As Usual group; SIMD – Scottish Index of Multiple Deprivation (there was a small amount of missing data, 4 in each group)

* Baseline caries (d3mft) data were not available for three children (one in the FV and two in the TAU group) due to issues with the dental inspection forms.

Table 6.2 Number of children by nursery and study arm

NHS Board	Nursery code (N = 39 nurseries)	FV (n = 265)	TAU (n = 269)	TOTAL (n = 534)
NHS Lothian	**201**	13	12	25
(21 nurseries, 297 children across the two arms)	**203**	4	5	9
	204	9	10	19
	205	5	6	11
	206	4	2	6
	208	5	7	12
	209	6	5	11
	216	7	8	15
	217	6	6	12
	222	2	3	5
	223	2	2	4
	224	7	6	13
	225	6	8	14
	226	13	13	26
	227	3	3	6
	228	8	8	16
	229	19	18	37
	230	4	4	8

NHS Board	Nursery code (N = 39 nurseries)	FV (n = 265)	TAU (n = 269)	TOTAL (n = 534)
	231	4	3	7
	232	9	9	18
	233	12	11	23
	Sub-total	148	149	297
NHS Fife	**301**	12	11	23
(9 nurseries, 121 children across the two arms)	**302**	8	8	16
	303	8	8	16
	304	2	1	3
	305	12	11	23
	306	8	8	16
	307	6	7	13
	308	2	3	5
	309	3	3	6
	Sub-total	61	60	121
NHS Tayside	**401**	11	12	23
(9 nurseries, 116 children across the two arms)	**402**	6	5	11
	403	7	9	16
	404	9	8	17
	405	7	9	16
	406	2	2	4
	407	2	5	7
	408	4	3	7
	409	8	7	15
	Sub-total	56	60	116

6.3 Parental questionnaire response rate

The response rates for all three rounds of the quality of life and resource use data collection are presented in Table 6.3 and Figure 6.1. The response rate for all three participating Health Boards combined was 75%, 59% and 57%, at baseline, 12-months and 24-months respectively (as the proportion of the questionnaires distributed at the baseline).

Table 6.3 Quality of life and resource use data collection questionnaire response rates

NHS Board	Baseline			12-month				24-month			
	Q-res distri-buted	Q-res returned		Q-res distri-buted	Q-res returned			Q-res distri-buted	Q-res returned		
	N baseline	n	% of N base	N 12-mo	n	% of N 12-mo	% of N base	N 24-mo	N	% of N 24-mo	% of N base
Fife	121	92	76%	113	60	53%	50%	111	63	57%	52%
Lothian	297	214	72%	293	178	61%	60%	270	164	61%	55%
Tayside	116	92	79%	119	77	65%	66%	112	79	71%	68%
Total	534	398	75%	525	315	60%	59%	493	306	62%	57%

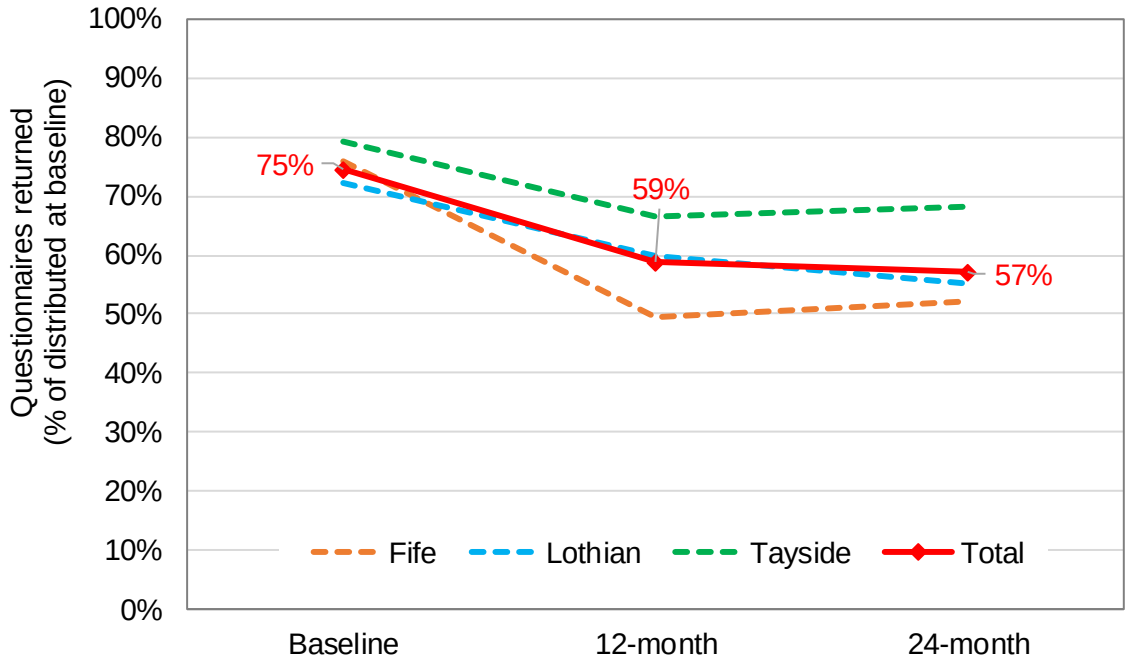

Figure 6.1 Parental questionnaires response rate

6.4 Missing data

Approximately 24%-31% of the each collected resource use item data were missing at baseline, 39%-45% at the 12-month and 41%-44% at the 24-month data collection point. Baseline questionnaire refers to the 12 months period prior to the baseline questionnaire distribution. Missing data were mostly due to non-return of the questionnaires by the participants, however, in a small number of cases specific item data were missing (e.g. due to ineligible information entered

in the response field) or a whole section of a questionnaire was missing. The intervention group had a slightly higher proportion of missing data at each assessment point than the control group: approximately 3%-5% higher, depending on a variable. The number and percentage of missing data for each collected resource use item for the intervention and control groups at baseline, 12, and 24 months are shown in Appendix 17.

In relation to the percentage of missing data at the level at which multiple imputations were performed (i.e. after the mean imputation of baseline values and mean imputation of single missing recourse use items had been conducted), 39%-45% of the data was missing for the combined resource use costs, 40%-45% for utility values and 0.4%-6% for the dental index (d3mft) (see Appendix 18). There were no missing intervention costs due to the methodology used.

6.5 Costs

6.5.1 Intervention costs

The average cost per child per visit in the FV group is shown in Figure 6.2. The major component was staff labour, which accounted for 64% (£7.59), followed by disposables (20%, £2.32).

The mean intervention cost per child in the FV group over the whole course of the study was £32.66 (SD £13.21).

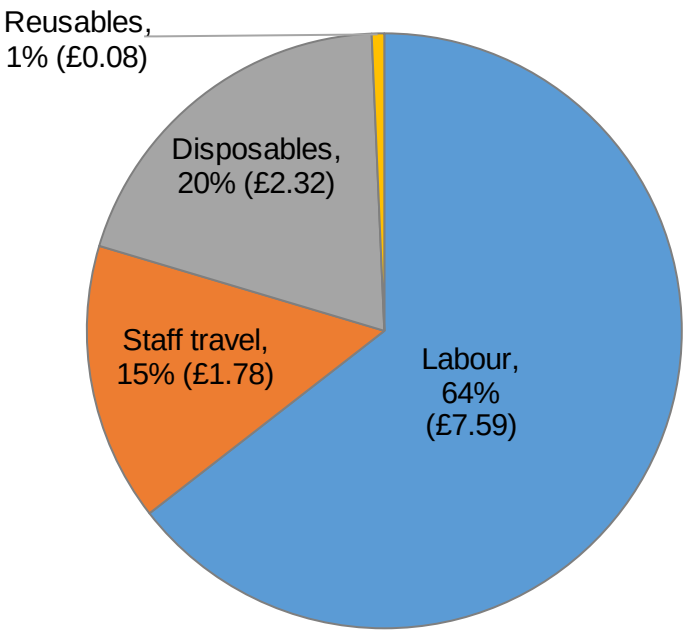

Figure 6.2 Average cost per FV group child per visit by intervention cost component

6.5.2 Resource use and costs

Table 6.4 reports the use of each resource item (mean number of visits, standard deviation, median, min and max) at baseline, 12- and 24-month follow-up in the intervention and the control group. There were no statistically significant differences in the use of each resource item between the groups, apart from one item. The only item with a statistically significant difference in the means between the two study groups was the number of dental hygienist appointments at the baseline. However, there were very low numbers of observations with a non-zero and non-missing values for dental hygienist: six in the FV (intervention) group and 17 respondents in the TAU (control) group at the baseline. The individual non-missing and non-zero values for the number of dental hygienist appointments at the baseline data collection were either “1” or “2” in both study groups.

Table 6.5 presents participant healthcare resource use costs by item by study group, at 12 months, whereas Table 6.6 shows the same for the 24 months data collection point. There were several outliers with a high number of speech and language therapist contacts. The parents of these children reported weekly appointments with a speech and language therapist throughout the whole reporting year. At 12 months, there were three outliers in the FV group and one

outlier in the TAU group. At 24 months, there was one outlier in the FV group and none in the TAU group.

Table 6.4 NHS and social care resource use per participant at baseline, 12- and 24-months (available case)

	FV (n=265)						TAU (n=269)						
Variable	**N**	**Mean**	**SD**	**Median**	**Min**	**Max**	**N**	**Mean**	**SD**	**Median**	**Min**	**Max**	**p-value ***
Baseline													
GP	186	1.95	2.20	1	0	12	199	1.89	2.98	1	0	35	0.84
A&E	188	0.27	0.53	0	0	2	204	0.22	0.58	0	0	4	0.39
Dentist	184	1.42	0.78	2	0	4	199	1.44	0.96	2	0	6	0.74
Hygienist (dental)	190	0.04	0.22	0	0	2	202	0.12	0.42	0	0	2	0.01
Speech therapist	188	0.34	1.51	0	0	14	201	0.23	1.19	0	0	12	0.44
Inpatient stay	189	0.07	0.39	0	0	4	204	0.16	1.32	0	0	17	0.34
Outpatient stay	189	0.12	0.56	0	0	6	204	0.11	0.76	0	0	10	0.90
12-months													
GP	146	1.60	1.50	1	0	8	159	1.64	1.87	1	0	14	0.84
A&E	147	0.24	0.53	0	0	3	162	0.23	0.64	0	0	3	0.88
Dentist	146	1.57	0.87	2	0	4	158	1.68	1.16	2	0	8	0.34
Hygienist (dental)	148	0.07	0.33	0	0	2	163	0.07	0.35	0	0	2	0.92
Speech therapist	148	1.41	7.26	0	0	52	163	0.80	4.63	0	0	52	0.38
Inpatient stay	148	0.15	0.94	0	0	10	163	0.13	1.13	0	0	14	0.89
Outpatient stay	148	0.14	0.66	0	0	7	163	0.27	1.31	0	0	12	0.25
24-months													
GP	147	1.19	1.27	1	0	6	159	1.10	1.36	1	0	7	0.54
A&E	147	0.23	0.52	0	0	2.5	158	0.18	0.42	0	0	2	0.35
Dentist	147	1.70	0.90	2	0	6	159	1.69	0.79	2	0	5	0.85

	FV (n=265)						TAU (n=269)						
Variable	**N**	**Mean**	**SD**	**Median**	**Min**	**Max**	**N**	**Mean**	**SD**	**Median**	**Min**	**Max**	**p-value ***
Hygienist (dental)	147	0.07	0.33	0	0	2	158	0.14	0.49	0	0	3	0.17
Speech therapist	147	0.62	4.41	0	0	52	158	0.22	1.23	0	0	12	0.30
Inpatient stay	147	0.08	0.49	0	0	4	158	0.05	0.32	0	0	3	0.52
Outpatient stay	147	0.15	0.58	0	0	5	158	0.19	1.30	0	0	15	0.72

* Two-sided p-value. SD – standard deviation.

Table 6.5 Participant healthcare resource use costs by item by study group, at 12 months

Participant healthcare resource use item	FV group, costs (£)								TAU group, costs (£)							
	N	Mean	SD	Min	Max	P25	Median	P75	N	Mean	SD	Min	Max	P25	Median	P75
GP	148	59.60	55.20	0	296.00	18.5	37	74	164	61.37	68.09	0	518.00	0	37	92.5
A&E	148	48.47	103.16	0	576.99	0	0	0	164	47.61	123.61	0	576.99	0	0	0
Dentist	148	41.10	22.56	0	104.52	26.13	52.26	52.26	164	44.12	29.79	0	209.04	26.13	52.26	52.26
Dental hygienist	148	0.48	2.14	0	12.92	0	0	0	164	0.51	2.34	0	12.92	0	0	0
S&L therapist	148	134.03	688.77	0	4,935.32	0	0	0	164	81.77	443.76	0	4,935.32	0	0	0
S&L therapist - without outliers *	145	37.31	137.58	0	949.10	0	0	0	163	52.00	227.67	0	1,898.20	0	0	0
Hospital inpatient	148	59.15	372.35	0	3,979.00	0	0	0	164	60.90	459.49	0	5,570.60	0	0	0
Hospital outpatient	148	26.78	130.06	0	1,387.40	0	0	0	164	55.71	260.44	0	2,378.40	0	0	0
"Other" items	148	5.75	36.51	0	273.25	0	0	0	164	12.94	121.41	0	1,500.00	0	0	0

Note: GP – general practitioner; A&E – accidents and emergency; S&L – speech and language; SD – standard deviation.
* Outliers are children with weekly appointments with a speech and language therapist throughout the reporting year. There were three outliers in the FV group and one outlier in the TAU group.

Table 6.6 Participant healthcare resource use costs by item by study group, at 24 months

Participant healthcare resource use item	FV group, costs (£)								TAU group, costs (£)							
	N	Mean	SD	Min	Max	P25	Median	P75	N	Mean	SD	Min	Max	P25	Median	P75
GP	147	44.05	46.81	0	222.00	0	37	74	159	40.61	50.28	0	259.00	0	37	74
A&E	147	45.14	100.86	0	480.83	0	0	0	159	35.08	80.55	0	384.66	0	0	0
Dentist	147	44.53	23.48	0	156.78	26.13	52.26	52.26	159	44.04	20.66	0	130.65	26.13	52.26	52.26
Dental hygienist	147	0.48	2.15	0	12.92	0	0	0	159	0.89	3.12	0	19.38	0	0	0
S&L therapist	147	58.75	418.94	0	4,935.32	0	0	0	159	21.19	116.07	0	1,138.92	0	0	0
S&L therapist - without outliers *	146	25.35	107.66	0	949.10	0	0	0	No outliers							
Hospital inpatient	147	32.48	194.88	0	1,591.60	0	0	0	159	20.02	125.02	0	1,193.70	0	0	0
Hospital outpatient	147	29.66	114.48	0	991.00	0	0	0	159	37.40	256.36	0	2,973.00	0	0	0
"Other" items	147	5.62	33.73	0	295.80	0	0	0	159	10.18	45.82	0	298.35	0	0	0

Note: GP – general practitioner; A&E – accidents and emergency; S&L – speech and language.
* Outliers are children with weekly appointments with a speech and language therapist throughout the reporting year. There was one outlier in the FV group and no outliers in the TAU group.

Table 6.7 shows other services used by the participants in each arm. The services listed under "other" category differed substantially between the groups, so they were costed individually. The unit costs assigned to each service item and the sources of the information used are listed in Appendix 19.

Table 6.7 "Other" resource use items indicated by respondents, by intervention group, by round of data collection

Baseline data collection			
TAU	**No**	**FV**	**No**
Asthma Clinic	1	Asthma outpatient clinic	3
Eye Hospital	7	Eye Hospital / eye pavilion	9
Health Visitor	1+ (1)	Health Visitor	13 (2)
Vaccination (various wording)	5	Health visitor (vaccination boosters)	1
Paediatrician	3	Paediatrician	2
Services different between the 2 arms:			
Allergy Clinic	1	Childsmile Nurse	2
Dental hospital	1	Edinburgh Cleft Team	1
Dietician	2	Eye Clinic	1
health centre	4	NHS 24 - out of hours	1
Hospital Dietician	2	Optician	3
Plastic surgeon	3	Physio	5.5
Sleep therapist	12	Yorkhill Children's Hospital	4
Tissue viability clinic	8		
12-months data collection			
(There were no identical or similar "Other" listings between the two arms at 12-months data collection.)			
TAU	**No**	**FV**	**No**
CF clinic	12	At nursery getting teeth checked	1
Children's ward - high temp	1	Dental hospital	2
Childsmile	2	Health visitor	5
Eye clinic review / Orthoptics	3	NHS24 phone call	1
Inpatient stay (2nd)		Osteopath	3.5
Play therapy	30	Outpatient clinic (hospital)	2
		Physio	1
24-months data collection			
TAU	**No**	**FV**	**No**
Eye Clinic / Eye hospital / Eye test / Optician / Optometrist / Given glasses	22	Eye outpatient clinic / Eyes	2

Services different between the 2 arms:

Child Community Health	2	Audiology	3
Routine consultant appointment	1	Childsmile / Childsmile at own dentist	2+ (3)
School dental service	1	Dermatology	2
		NHS 24	1
		Nurse	1
		Paediatrician	3
		Pharmacist	1

Notes: 1) One respondent didn't indicate the number of health visitor contacts. 2) One respondent indicated 12 health visitor contacts. Some of the health visitor contacts might have been vaccination visits. 3) One respondent didn't indicate the number of Childsmile contacts.

Table 6.8 compares the mean total cost per participant over the 24-month follow-up between the groups. The total cost per participant includes the total cost of health care resources used over the two-year duration of the study but excludes "other" resource use items – for both groups, and, additionally, the intervention group (FV) total cost includes the total intervention cost. Medications were not included in the total resource use due to the similar amount of use between the groups and the difficulty matching unit cost with the inconsistent free-text reporting of the medications used (see section 6.7 Medication use).

In both cases, the available case analysis and multiple-imputed dataset analysis, general linear modelling with gamma family and identity link was used, adjusted for sex, age, deprivation, baseline utility and caries at baseline. The available case analysis resulted in the mean total cost per participant of £561.08 for the intervention group and £487.85 for the control group in (i.e. the difference of £73.23). The results of the analysis of multiple-imputed dataset were £665.90 for the FV group and £597.52 for the TAU group (the difference of £68.37). However, in both cases the differences were not statistically significant.

Table 6.8 Total cost per participant over the 24-month follow-up

	Mean	SE	95% CI lower	95% CI upper	p-value
Available case (adjusted)					
FV (intervention)	561.08	48.92	391.98	583.73	0.189
TAU (control)	487.85	61.07	441.39	680.77	
MI (adjusted)					
FV (intervention)	665.90	70.67	458.45	736.59	0.382
TAU (control)	597.52	70.74	526.97	804.83	

Notes: 1) The total cost per participant includes the total cost of health care resources used over the two-year duration of the study but excludes "other" resource use items – for both groups, and, additionally, the intervention group (FV) total cost includes total intervention cost. 2) General linear modelling with gamma family and identity link was used. 3) Adjusted for sex, age, deprivation, baseline utility and caries at baseline. 4) Second year QALYs were discounted at 1.5% discount rate. 5) MI: multiple imputation with chained equations.

6.6 CHU9D utility scores

The CHU9D health utility values for each treatment group at baseline, 12, and 24 months are shown in Table 6.9 (available case), Table 6.10 (after imputation) and visualized in Figure 6.3 (after imputation) assuming a linear change between each assessment point.

The completeness at baseline was 70% (185/265) for the intervention group and 74% (200/269) for the control group. Completeness rate fell over time in both groups: at 12-month follow-up it was 56% (148/265) for FV, and 59% (159/269) for TAU; at 24-month follow-up it was 55% (147/265) and 58% (157/269), respectively.

The baseline utility was almost the same for the two groups, with a difference of 0.005 (Table 6.10). The utility values for the control (TAU) group increased slightly over the 24 months from 0.937 to 0.943, whereas the utility of the intervention group almost stayed the same: 0.938 at baseline, 0.939 at 24 months (imputed dataset values). There were no statistically significant differences between the groups at baseline, 12 and 24 months. The differences in utility values between the FV and TAU groups were very small (i.e. -0.003 at 12 months, and -0.004 at 24 months), given the full range of CHU9D index score being 0 (worst) to 1 (full health).

Table 6.9 CHU9D utility value (available case)

Variable	N	Mean	SD	Median	Min	Max	P-value
Index score							
Baseline utility, FV	185	0.938	0.065	0.952	0.572	1	0.92
Baseline utility, TAU	200	0.937	0.061	0.952	0.698	1	
12-mo utility, FV	148	0.942	0.065	0.952	0.666	1	0.71
12-mo utility, TAU	159	0.944	0.059	0.952	0.757	1	
24-mo utility, FV	147	0.942	0.065	0.952	0.696	1	0.59
24-mo utility, TAU	157	0.946	0.062	0.952	0.643	1	
Utility change							
12-mo minus Baseline, FV	119	0.001	0.063	0.000	-0.197	0.178	0.59
12-mo minus Baseline, TAU	140	0.005	0.068	0.000	-0.243	0.195	
24-mo minus Baseline, FV	123	0.006	0.084	0.000	-0.193	0.428	0.47
24-mo minus Baseline, TAU	142	0.013	0.073	0.000	-0.182	0.212	

Note: The total numbers of observations were: 265 for FV group and 269 for TAU group.

Table 6.10 CHU9D utility value (after imputation)

Variable	Mean	SE	95%CI lower	95%CI upper	p-value
Baseline utility, FV	0.938	0.003	0.931	0.944	0.92
Baseline utility, TAU	0.937	0.003	0.931	0.943	
12-mo utility, FV	0.941	0.005	0.932	0.951	0.64
12-mo utility, TAU	0.944	0.004	0.936	0.953	
24-mo utility, FV	0.939	0.005	0.930	0.949	0.54
24-mo utility, TAU	0.943	0.005	0.934	0.952	

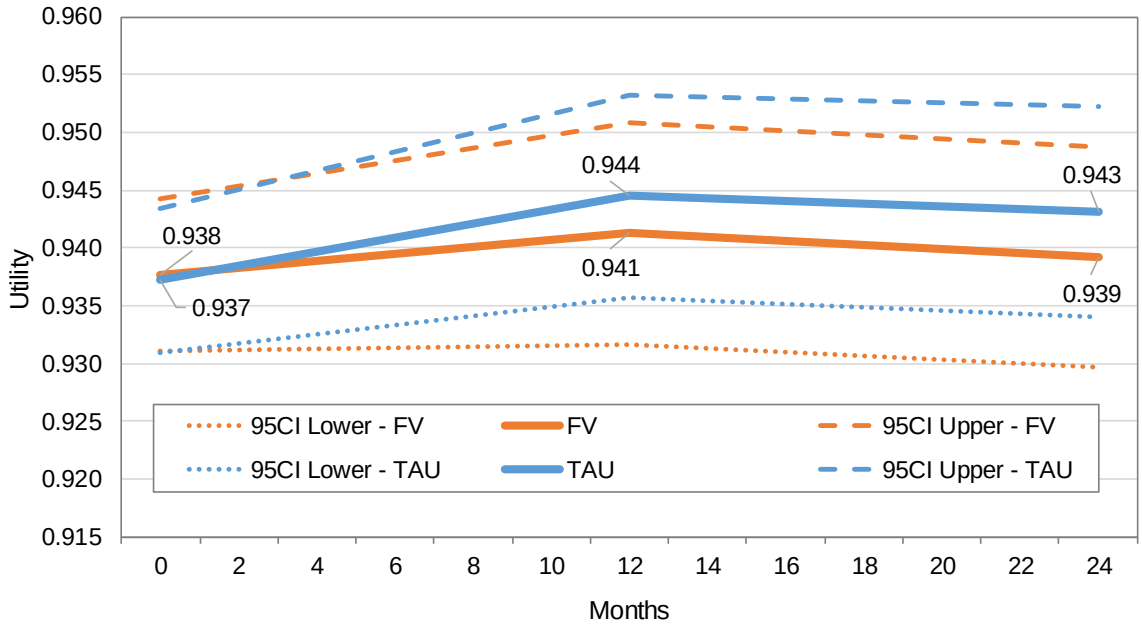

Figure 6.3 CHU9D utility values at baseline, 12, and 24 months (after imputation)

QALYs gained per participant over the 24-month follow-up are shown in Table 6.11. Both in the available case analysis (the difference of -0.008) and in the case of multiple-imputed dataset (the difference of -0.004) there was no statistically significant difference between the groups.

Table 6.11 QALY gained per participant over the 24-month follow-up

	Mean	SE	95% CI lower	95% CI upper	p-value
Available case (adjusted)					
FV (intervention)	1.8525	0.0144	1.8243	1.8807	0.568
TAU (control)	1.8603	0.0125	1.8358	1.8848	
MI (adjusted)					
FV (intervention)	1.8590	0.0078	1.8489	1.8780	0.636
TAU (control)	1.8634	0.0074	1.8437	1.8743	

Notes: General linear modelling with gamma family and log link was used. Adjusted for sex, age, deprivation, baseline utility and caries at baseline. MI: multiple imputation with chained equations. Second year QALYs were discounted at 1.5% discount rate.

6.7 Medication use

The numbers of study participants who used and did not use any medication are shown in Table 6.12. The amount of medication use was similar between the groups, hence it was decided not to include medication costs into the total resource use cost. In addition, it would be difficult to match unit cost with the inconsistent free-text reporting of medications used.

Table 6.12 Medication used (yes/no) by treatment group

	Yes		No (or missing)		Total
FV (intervention)					
Baseline	127	69%	58	31%	185
12-mo	90	62%	55	38%	145
24-mo Paper	75	61%	48	39%	123
24-mo Online	19	86%	3	14%	22
TAU (control)					
Baseline	122	64%	68	36%	190
12-mo	93	60%	62	40%	155
24-mo Paper	79	61%	51	39%	130
24-mo Online	24	96%	1	4%	25

6.8 Cost-utility analysis

This section presents the results of the cost-utility analysis (CUA), including base-case analysis and probabilistic sensitivity analysis.

6.8.1 Cost-utility base-case analysis

The cost-utility base-case analysis results for the PT@3 FV intervention are presented in Table 6.13. The intervention group incurred higher costs within the 24-month time horizon, while generating marginally less QALYs, than the control arm. However, these differences were not statistically significant for both costs and QALYs. The average cost per patient was £665.90 (95%CI £564.38, £752.84) in the intervention group and £597.52 (95%CI £519.29, £674.27) in the control group. Compared to the control group the intervention group had an incremental cost of £68.37 (95%CI -£18.04, £143.82; p = 0.382). The average QALYs gained were 1.8590 (95%CI 1.8483, 1.8674) for the intervention group and 1.8634 (95%CI

1.8522, 1.8729) for the control group. The intervention group had a marginal incremental QALY loss: -0.0044 (95%CI -0.016, 0.0069), p = 0.636, compared to the control group.

Table 6.13 Cost-utility results (after imputation) with 24-month follow-up

Treatment group	Cost (£)			QALY		
	Mean	**SE**	**95%CI**	**Mean**	**SE**	**95%CI**
FV (intervention)	665.90	70.74	564.38, 752.84	1.8590	0.0078	1.8483, 1.8674
TAU (control)	597.52	70.67	519.29, 674.27	1.8634	0.0074	1.8522, 1.8729
Difference	68.37	**p-value:** 0.382	-18.04, 143.82	-0.0044	**p-value:** 0.636	-0.016, 0.0069
ICER	Dominated*					

Notes: * With very small numerical differences in effect in favour of TAU and TAU being less costly than FV, the ICER is calculated as dominated. However, this calculation is based on non-statistically significant differences in outcomes between FV and TAU.

1) The total cost per participant includes the total cost of health care resources used over the two-year duration of the study but excludes "other" resource use items – for both groups, and, additionally, the intervention group (FV) total cost includes total intervention cost. 2) General linear modelling was used. 3) Both cost and QALY were adjusted for sex, age, deprivation, baseline utility and caries at baseline. 4) Second year costs and QALYs were discounted at 1.5% discount rate.

The cost-effectiveness plane for the base-case analysis is shown in Figure 6.4. The dyads come from the 1000 bootstrap iterations. The X-axis represents the bootstrapped incremental QALYs between the intervention and control groups and the Y-axis represents the incremental costs. The vast majority of the simulated cost-utility dyads are above the X-axis, indicating that the intervention was more expensive comparted to the control. Likewise, the majority of the simulated cost-utility dyads are to the left of the Y-axis, indicating that the intervention was unlikely to improve quality of life outcomes. The fact that the majority of the dyads are situated in the north-west quadrant means that in the majority of the bootstrap iterations TAU dominates: namely, the FV intervention is less effective (in terms of QALY gained) and more costly than TAU. The flat oval shape of the cost effectiveness plane indicates that there is a higher degree of uncertainty surrounding the estimates of the incremental QALYs than the incremental cost.

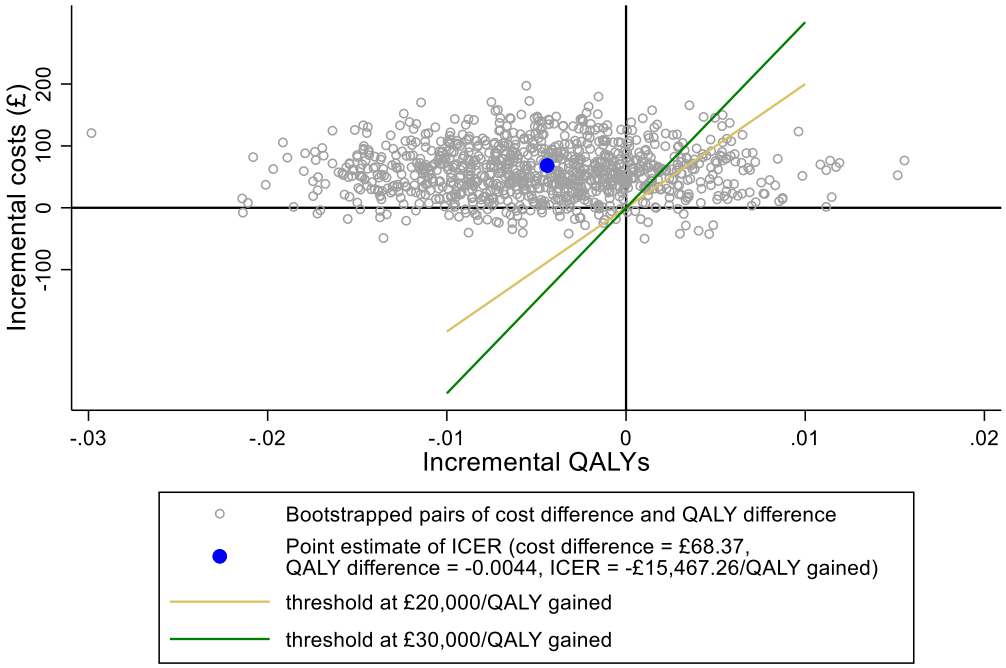

Figure 6.4 Cost-effectiveness plane representing 1000 bootstrapped cost difference and QALY difference pairs

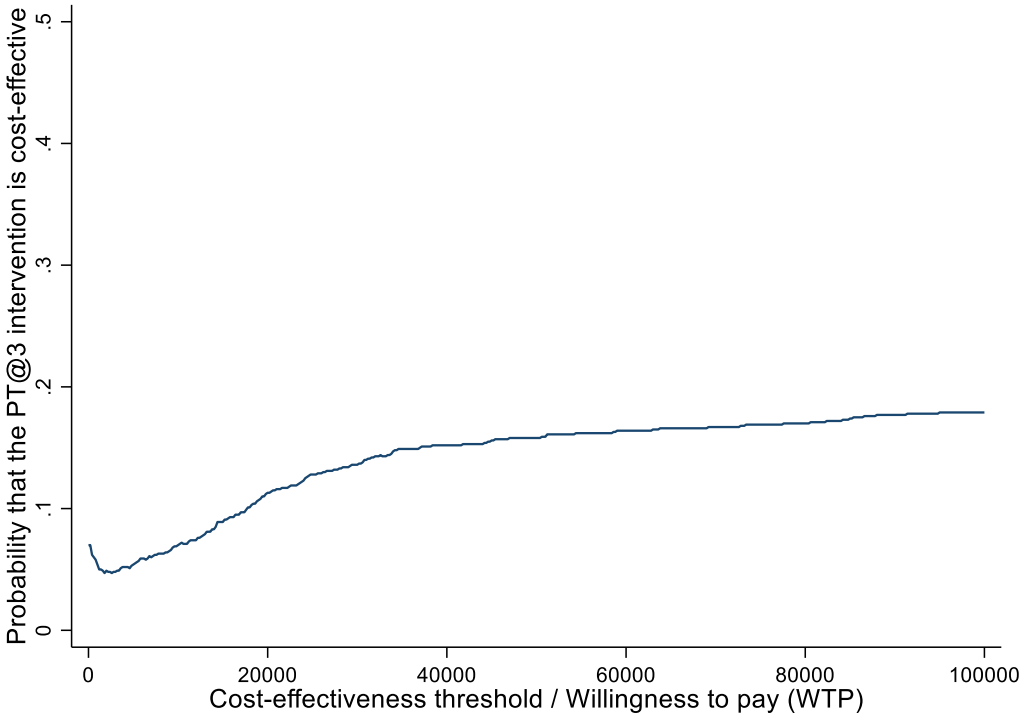

Figure 6.5 Cost-effectiveness acceptability curve (CEAC)

The cost-effectiveness acceptability curve (CEAC) for the base-case analysis is shown in Figure 6.5. The probability that the intervention was cost-effective at the £20,000 threshold was 11.3%, and at the £30,000 threshold it was 13.6%. From Figure 6.4, this corresponds to the proportion of dyads under the sand

colour line (£20,000/QALY gained threshold) and under the green line (£30,000/QALY gained threshold) on the cost-effectiveness plane, respectively.

6.8.2 Cost-utility sensitivity analyses

Results for the sensitivity analysis are presented in Table 6.14. In all scenarios the intervention (FV) was more costly and gained less QALYs than the control (TAU). Similarly, in all scenarios the probability of the intervention being cost effective (at the £20,000/QALY gained threshold) was low, with the highest being 19.8% in the available case scenario (SA7) and 18.2% in the scenario when "other" resource use costs were included (SA2).

Table 6.14 Sensitivity analyses results (after imputation) with 24-month follow-up

Analysis	**Incremental cost** (Intervention minus Control) **(95% CI)**	**Incremental QALY** (Intervention minus Control) **(95% CI)**	**ICER (£/ QALY gained)**	**Probability of being C-E at £20,000/QALY gained threshold (%)**
Base-case	68.37 (-18.04, 143.82)	-0.0044 (-0.016, 0.0069)	-15,467.26	11.3
SA1: Intervention costs (of "mock" application delivery) added to TAU arm children	36.64 (-48.51, 111.47)	-0.0044 (-0.016, 0.0069)	-8,288.66	17.1
SA2: "Other" resource use costs included into total cost	54.98 (-31.03, 130.76)	-0.0044 (-0.016, 0.0069)	-12,437.51	18.2
SA3: Intervention costs are 30% less than in base-case	58.11 (-26.34, 132.39)	-0.0044 (-0.016, 0.0069)	-13,145.57	12.5
SA4: Intervention costs are 30% greater than in base-case	78.60 (-7.17, 154.71)	-0.0044 (-0.016, 0.0069)	-17,780.01	9.2
SA5: Discount rate of 3.5%	67.27 (-36.78, 126.82)	-0.0044 (-0.016, 0.007)	-15,408.75	14.7
SA6: Societal perspective – parental time off work included	54.44 (-70.35, 167.84)	-0.0044 (-0.016, 0.0069)	-12,315.31	16.1
SA7: Available case analysis	73.23 (-31.60, 188.38)	-0.0078 (-0.2092, 0.0254)	-9,378.60	19.8
SA8: Four outliers removed (with more than 45 Speech and Language Therapist contacts in a 12-mo. period)	16.45 (-40.49, 75.70)	-0.0060 (-0.0197, 0.0056)	-2,736.05	13.7

Note: SA – sensitivity analysis. 1) General linear modelling was used. 2) Both cost and QALY were adjusted for sex, age, deprivation, baseline utility and caries at baseline. 3) Second year costs and QALYs were discounted at 1.5% (SA1-SA4, and SA6-SA8) or 3.5% discount rate (SA5).

6.8.3 Subgroup analysis

Two types of subgroup analyses were planned *a priori*: a) by deprivation; and b) by presence/absence of caries at the baseline. However, it was not possible to meaningfully run either of them due to low numbers in the relevant subgroups within the EE sample: a) there were only 40 children in SIMD1 across the two study groups, 190 in SIMD2, 149 in SIMD3, 93 in SIMD4, and 61 in SIMD5 (SIMD was unknown for 1 child); b) there were only 75 children with caries at the baseline (37 in the FV group and 38 in the TAU group).

6.9 Cost-effectiveness analysis

The cost-effectiveness results based on the d3mft effectiveness measure are presented in Table 6.15. As was described earlier, in the base-case cost-utility analysis section, the intervention was more costly within the 24-month time horizon. The average cost per patient was £665.90 (95%CI £564.38, £752.84) in the intervention group and £597.52 (95%CI £519.29, £674.27) in the control group. The intervention group had an incremental cost of £68.37 (95%CI -£18.04, £143.82) greater than the control group (p = 0.382).

The d3mft effectiveness data were analysed using a “difference in difference” approach. A positive d3mft difference means worsening of the oral health state. Table 6.15 shows that the mean d3mft difference was higher in the FV group, in comparison with the TAU group, indicating that on average the intervention arm children had a slightly greater worsening of the d3mft. The difference in difference was 0.071, although the difference between the groups was not statistically significant (p = 0.671), with a wide 95% confidence interval, which included zero (-0.237, 0.406).

Table 6.15 Cost-effectiveness results on d3mft, with 24-month follow-up

Treatment group	Cost (£)			d3mft difference (d3mft 24mo. – d3mft 0 mo.)		
	Mean	SE	95%CI	Mean	SE	95%CI
FV (intervention)	665.90	70.74	564.38, 752.84	0.992	0.118	0.761, 1.239
TAU (control)	597.52	70.67	519.29, 674.27	0.921	0.118	0.695, 1.148
Difference	68.37	**p-value:** 0.382	-18.04, 143.82	0.071	**p-value:** 0.671	-0.237, 0.406
ICER	Dominated:	The intervention was more costly and less effective (it had larger worsening of d3mft).				

Notes: 1) The total cost per participant includes the total cost of health care resources used over the two-year duration of the study but excludes "other" resource use items – for both groups, and, additionally, the intervention group (FV) total cost includes total intervention cost. 2) General linear modelling was used. 3) Both cost and d3mft difference were adjusted for sex, age, deprivation, baseline utility and caries at baseline. 4) Cost analysis was conducted on a multiple-imputed dataset (n=534). 5) d3mft was analysed on a complete case dataset (n=508 (95%) out of 534). 6) Second year costs were discounted at 1.5% discount rate.

The cost-effectiveness plane with d3mft difference in difference as an effectiveness measure is shown in Figure 6.6. Positive values along the X-axis (incremental d3mft) mean the worsening of the dental outcome, therefore the quadrants differ from the usual quadrant representation. Here, the North-East quadrant means that the intervention (FV) is dominated (it costs more and is less effective). The majority of bootstrapped pairs lay in this North-East quadrant 655 (66%) out of 1,000. The South-East quadrant means that FV is less costly and less effective; 31 (3%) bootstrapped pairs. The South-West quadrant means that FV dominates (it costs less and is more effective); only 22 (2%) pairs lay here. While the North-West quadrant means that FV is more costly and more effective; 292 (29%) pairs. It was not possible to construct a CEAC, as no accepted threshold values exist for d3mft.

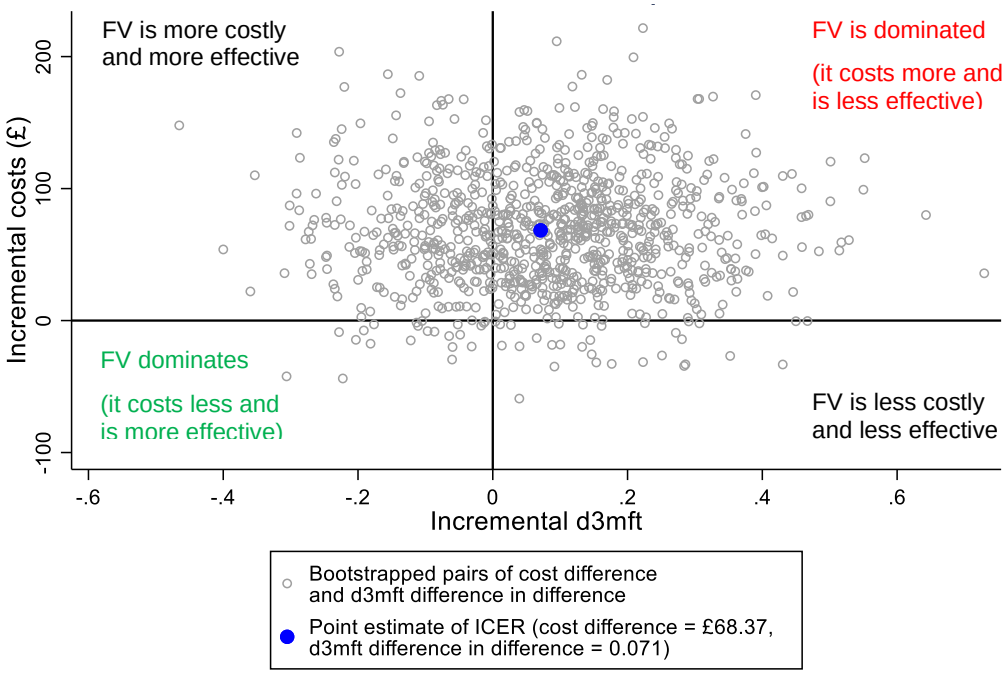

Figure 6.6 Cost-effectiveness plane representing 1000 bootstrapped cost difference and d3mft difference in difference pairs

Note: FV – fluoride varnish (intervention). Positive values along the X-axis (incremental d3mft) mean the worsening of the dental outcome, therefore the quadrants differ from the usual quadrant representation. Here, North-West quadrant = FV is more costly and more effective; North-East = FV is dominated (it costs more and is less effective); South-East = FV is less costly and less effective; and South-West = FV dominates (it costs less and is more effective).

6.10 Cost-consequence analysis

The results of the cost-consequence analysis (CCA) are shown in Table 6.16. None of the cost or outcome differences between the two groups were statistically significant. In the base-case scenario, the mean total cost per child in the intervention group (which included intervention cost and participants' NHS resource use costs) was £68.37 higher than in the control group. When "other" NHS resources costs were added to the total cost (as per the sensitivity analysis scenario SA2 described in Sections 5.3.5.2 and 6.8.2 earlier) this difference reduced to £54.98.

With regard to OH/GHQoL, the mean differences between the groups were mostly negative indicating that the children in the FV group had marginally worse OH/GHQoL at 24 months (although the differences were not statistically significant). The exceptions were the PedsQL school domain score where the difference was positive, and SOHO-5 score, where the negative difference means

that the intervention group children had slightly better OHQoL (due to reversed scoring).

The FV group had marginally better dental health, i.e. lower mean d3mft, both at the baseline and at 24 months (again, the differences between the two groups were not statistically significant).

Table 6.16 Results of cost-consequence analysis

Costs / Outcomes	FV (intervention)	TAU (control)	Difference
Costs (MI dataset)	**Mean (95% CI), £**	**Mean (95% CI), £**	**Mean (95% CI), £**
Total cost (base-case)	665.90 (564.38, 752.84)*	597.52 (519.29, 674.27)*	68.37 (-18.04, 143.82)*
Total cost, including "other" resources cost	674.16 (574.39, 764.51)*	619.18 (536.89, 701.59)*	54.98 (-31.03, 130.76)*
Outcomes / Consequences	**Mean (95% CI)**	**Mean (95% CI)**	**Mean (95% CI)**
QALY (MI dataset)	1.8590 (1.8483, 1.8674)*	1.8634 (1.8522, 1.8729)*	-0.0044 (-0.016, 0.0069)*
Dental health (ACA)			
d3mft at 0 mo.	0.428 (0.257, 0.599)	0.498 (0.298, 0.698)	-0.07 (-0.333, 0.193)
d3mft at 24 mo.	1.371 (1.062, 1.681)	1.375 (1.029, 1.722)	-0.004 (-0.467, 0.459)
d3mft difference, unadjusted (d3mft at 24 mo. minus d3mft at 0 mo.)	1.016 (0.767, 1.264)	0.913 (0.678, 1.148)	0.103 (-0.239, 0.444)
d3mft difference, adjusted (d3mft at 24 mo. minus d3mft at 0 mo.)	0.992 (0.761, 1.239)*	0.921 (0.695, 1.148)*	0.071 (-0.237, 0.406)*
	FV (intervention)	**TAU (control)**	**Difference**
	Mean (95% CI)	**Mean (95% CI)**	**Mean (95% CI)**
OHQoL outcomes at 24 mo. (ACA)			
PedsQL-OH score	95.4 (93.7, 97.1)	95.5 (94.2, 96.7)	-0.1 (-2.2, 2.0)
SOHO-5 score	0.3 (0.2, 0.4)	0.4 (0.2, 0.6)	-0.1 (-0.3, 0.1)
GHQoL outcomes at 24 mo. (ACA)			
Utility (CHU9D)	0.942 (0.932, 0.953)	0.946 (0.936, 0.956)	-0.004 (-0.018, 0.01)
PedsQL - Total score	88.2 (86.5, 89.9)	88.7 (87.0, 90.4)	-0.6 (-3.0, 1.9)
PedsQL - Physical domain score	92.1 (90.4, 93.8)	92.4 (90.4, 94.4)	-0.3 (-2.9, 2.4)
PedsQL - Emotional domain score	79.8 (77.3, 82.4)	80.0 (77.5, 82.5)	-0.2 (-3.7, 3.4)
PedsQL - Social domain score	88.6 (86.2, 91.0)	90.7 (88.6, 92.8)	-2.1 (-5.3, 1.1)
PedsQL - School	90.6	90.2	0.5

Costs / Outcomes	FV (intervention)	TAU (control)	Difference
domain score	(88.6, 92.7)	(88.1, 92.3)	(-2.5, 3.4)
PedsQL - Psycho-social domain	85.7 (83.7, 87.6)	86.5 (84.6, 88.3)	-0.8 (-3.5, 1.9)

Notes: CI – confidence interval; MI – multiple-imputed; ACA – available case analysis; OHQoL – oral health-related quality of life; GHQoL - general health-related quality of life.
* Bootstrapped confidence intervals. QALY: the more QALYs are acquired the better. d3mft: the higher the value, the worse is the dental health. CHU9D utility values range from 0 (dead) to 1 (perfect health). PedsQL and PedsQL-OH: The higher the 0-100 scale score, the better is the quality of life. SOHO-5: The lower the score, the better is the quality of life. The possible range is 0-28.

6.10.1 Exploratory comparative analysis of GHQoL and OHQoL measures at 24-months

The results of an exploratory comparative analysis of GHQoL and OHQoL measures at 24-months (end of study), as a part of CCA, are presented in the tables below.

Table 6.17 shows the end of study PedsQL Core scores by domain and by item (and the oral health add-on module is presented separately in Table 6.19). The study group means were not significantly different apart from one item where the p-value was approaching significance – "Other children not playing with him/her" (p = 0.052). The only other item with a p-value under 0.1 was "Getting teased by others" with p = 0.082. Both of these items are a part of the Social domain, and, as a consequence, this domain had the lowest p-value of all domains (p = 0.078). In this table, the higher the PedsQL 0-100 scale item/domain score, the better is the quality of life. A negative difference between the group means (Mean $_{FV}$ - Mean $_{TAU}$) indicates that the children in the FV group had worse GHQoL than the TAU children, while a positive difference in means indicates that FV children had better GHQoL than the TAU children. However, the values of the difference in means by item / by domain were small and ranged from -4.1 to 2.2.

Comparison of CHU9D scores by individual item and the utility index at the end of the study (24 months) is presented in Table 6.18. There are five levels of response in each CHU9D item, rated from 1 (does not affect the child at all) to 5 points (affects very much). The higher the CHU9D item score, the worse is the quality of life. A negative difference between the group means (Mean $_{FV}$ - Mean $_{TAU}$) indicates that the children in the FV group had better GHQoL than the TAU

children, while a positive difference in means indicates that FV children had worse GHQoL than the TAU children. The table shows that there was almost no difference between the study group means. All differences in means by item were within the range from -0.05 to 0.11, which is low taking in account that the full scale for each item is 1 to 5. None of these differences were statistically significant.

The utility index values range from 0 (dead) to 1 (perfect health). The mean utility of per child in the FV group was 0.94, and in the TAU group it was 0.95, with a p-value of 0.639, meaning the was no difference in utility between the groups at the 24-months data collection point.

The results for the OHQoL measures, PedsQL-OH and SOHO-5, are displayed in Table 6.19. The higher the PedsQL-OH 0-100 scale score, the better is the quality of life, hence, a positive difference in the means indicates that the FV-group children had better GHQoL than the TAU children. The values of the difference in the PedsQL-OH means by item and for the total OH score were small (ranged from -1.9 to 1.4) and non-significant.

The possible range of the total SOHO-5 score is 0 to 28. The lower the score, the better is the OHQoL. In the PT@3 Study, the means for both study groups equalled to zero for almost all items, apart from “Difficulty eating” (Mean $_{FV}$ = 0.2, Mean $_{TAU}$ = 0.3; p = 0.505). The medians for both groups for all items and the total score equalled to zero. The SOHO-5 total mean score was 0.3 for the FV group and 0.4 for the TAU group (p = 0.491).

Appendix 20 contains the results of primary endpoint analysis, and Appendix 21 presents the number needed to treat (NNT) and the relevant cost calculations, based on the economic evaluation cohort.

Table 6.17 Comparison of PedsQL scores at 24-months, by study group

PedsQL domain / Item	Arm	N	Mean	Std Dev	Median	Variance	WMW test results		Mean $_{FV}$ - Mean $_{TAU}$
							Z	Pr > |Z| *	
Total PedsQL score (without oral health add-on)	**FV**	144	88.2	10.3	90.5	106.5	-0.649	0.516	-0.6
	TAU	159	88.7	10.9	91.7	119.5			
Physical domain score	**FV**	144	92.1	10.5	96.7	109.9	-0.728	0.467	-0.3
	TAU	159	92.4	12.8	96.9	163.8			
Emotional domain score	**FV**	144	79.8	15.5	80.0	241.1	-0.166	0.868	-0.2
	TAU	159	80.0	15.9	80.0	251.3			
Social domain score	**FV**	144	88.6	14.5	95.0	209.8	-1.760	0.078	-2.1
	TAU	159	90.7	13.4	95.0	180.5			
School domain score	**FV**	143	90.6	12.6	100.0	160.0	0.281	0.779	0.5
	TAU	159	90.2	91.7	13.5	182.5			
Psycho-social domain	**FV**	144	85.7	11.8	88.5	140.2	-0.823	0.411	-0.8
	TAU	159	86.5	11.9	90.4	142.1			
Physical functioning									
Walking	**FV**	143	96.3	11.5	100.0	131.7	-0.903	0.366	-0.5
	TAU	159	96.9	13.7	100.0	187.8			
Running	**FV**	143	96.0	11.7	100.0	137.8	-1.224	0.221	-0.7
	TAU	159	96.7	13.5	100.0	182.9			
Participating in play/exercise	**FV**	144	94.4	14.0	100.0	196.2	-1.194	0.232	-1.3
	TAU	159	95.8	14.4	100.0	207.3			
Lifting something heavy	**FV**	143	93.0	14.4	100.0	206.0	-0.223	0.824	0.1
	TAU	159	92.9	16.4	100.0	270.0			
Bathing	**FV**	143	96.5	11.7	100.0	137.3	-0.439	0.661	0.0
	TAU	158	96.5	13.4	100.0	178.9			

PedsQL domain / Item	Arm	N	Mean	Std Dev	Median	Variance	WMW test results		Mean FV - Mean TAU
							Z	Pr > |Z| *	
Helping to pick up toys	**FV**	143	89.2	20.9	100.0	436.3	0.595	0.552	0.7
	TAU	158	88.4	20.5	100.0	419.1			
Hurts/aches	**FV**	144	83.7	21.2	100.0	448.6	-0.280	0.780	-0.7
	TAU	158	84.3	21.4	100.0	457.7			
Low energy	**FV**	144	88.7	17.7	100.0	313.2	0.546	0.585	1.1
	TAU	159	87.6	18.6	100.0	347.1			
Emotional functioning									
Feeling afraid/scared	**FV**	144	77.3	21.7	75.0	471.3	-1.155	0.248	-3.1
	TAU	159	80.3	20.4	75.0	414.3			
Feeling sad/blue	**FV**	143	80.4	19.3	75.0	370.9	0.305	0.760	0.7
	TAU	158	79.7	19.6	75.0	383.4			
Feeling angry	**FV**	144	75.2	20.6	75.0	423.9	0.499	0.618	1.6
	TAU	159	73.6	22.2	75.0	492.4			
Trouble sleeping	**FV**	144	84.2	21.3	100.0	452.3	-0.082	0.935	0.2
	TAU	159	84.0	21.8	100.0	476.9			
Worrying	**FV**	144	82.3	20.9	87.5	436.0	0.036	0.971	-0.1
	TAU	159	82.4	20.4	75.0	415.8			
Social functioning									
Playing with other children	**FV**	144	87.8	20.0	100.0	402.0	-0.696	0.486	-1.5
	TAU	159	89.3	19.2	100.0	367.6			
Other children not playing with him/her	**FV**	144	84.4	20.2	100.0	409.7	-1.947	0.052	-4.1
	TAU	159	88.5	17.7	100.0	314.4			
Getting teased by others	**FV**	144	86.8	18.0	100.0	322.9	-1.740	0.082	-3.3
	TAU	159	90.1	15.9	100.0	253.3			
Not able to do things other children can	**FV**	144	92.4	15.2	100.0	229.7	-0.098	0.922	0.4

PedsQL domain / Item	Arm	N	Mean	Std Dev	Median	Variance	WMW test results		Mean FV - Mean TAU
							Z	Pr > |Z| *	
do									
	TAU	159	92.0	16.5	100.0	271.5			
Keeping up when playing with other children	**FV**	142	91.7	17.3	100.0	299.0	-1.316	0.188	-1.8
	TAU	158	93.5	17.0	100.0	288.1			
School functioning									
Doing the same school activities as peers	**FV**	142	93.3	16.6	100.0	274.1	-1.305	0.192	-1.8
	TAU	158	95.1	14.8	100.0	218.6			
Missing school due to not feeling well	**FV**	143	87.8	17.5	100.0	306.9	0.907	0.364	2.2
	TAU	159	85.5	19.4	100.0	374.9			
Missing school to go to doctor/hospital	**FV**	143	90.9	15.0	100.0	224.9	0.323	0.747	1.0
	TAU	159	89.9	16.7	100.0	277.8			

Notes: WMW - Wilcoxon Mann-Whiney U-test (also known as Wilcoxon rank-sum test); * Two-sided p-value. The higher the PedsQL 0-100 scale item/domain score, the better is the quality of life.

Table 6.18 Comparison of CHU9D scores by individual item at 24-months, by study group

CHU9D item	Arm	N	Mean	Std Dev	Median	Variance	WMW test results		Mean $_{FV}$ minus Mean $_{TAU}$
							Z	Pr > |Z|*	
Worried	**FV**	147	1.15	0.50	1.00	0.25	0.645	0.519	0.05
	TAU	158	1.09	0.33	1.00	0.11			
Sad	**FV**	147	1.12	0.51	1.00	0.26	0.663	0.507	0.05
	TAU	158	1.07	0.32	1.00	0.10			
Pain	**FV**	147	1.10	0.32	1.00	0.10	-0.004	0.997	-0.01
	TAU	159	1.11	0.38	1.00	0.15			
Tired	**FV**	147	1.60	0.75	1.00	0.56	1.170	0.242	0.11
	TAU	159	1.48	0.64	1.00	0.42			
Annoyed	**FV**	147	1.20	0.49	1.00	0.24	-0.405	0.686	-0.01
	TAU	159	1.21	0.48	1.00	0.23			
School work / homework	**FV**	147	1.20	0.56	1.00	0.31	1.113	0.266	0.05
	TAU	158	1.15	0.52	1.00	0.27			
Sleep	**FV**	147	1.16	0.43	1.00	0.19	-1.137	0.256	-0.05
	TAU	159	1.21	0.48	1.00	0.23			
Daily routine	**FV**	147	1.22	0.53	1.00	0.28	0.581	0.561	0.03
	TAU	159	1.19	0.49	1.00	0.24			
Joining in activities	**FV**	147	1.16	0.45	1.00	0.20	0.715	0.475	0.00
	TAU	159	1.16	0.59	1.00	0.35			
Utility index	**FV**	147	0.94	0.07	0.95	0.00	-0.469	0.639	-0.01
	TAU	157	0.95	0.06	0.95	0.00			

Notes: WMW - Wilcoxon Mann-Whiney U-test (also known as Wilcoxon rank-sum test). * Two-sided p-value. There are five levels of response in each CHU9D item, rated from 1 (does not affect the child at all) to 5 points (affects very much). The higher the CHU9D item score, the worse is the quality of life. The utility index values range from 0 (dead) to 1 (perfect health).

Table 6.19 Comparison of oral health quality of life measures at 24-months, by study group

Questionnaire / Item	Arm	N	Mean	Std Dev	Median	Variance	WMW test results		Mean $_{FV}$ minus Mean $_{TAU}$
							Z	Pr > |Z| *	
PedsQL - OH									
Total OH Score (sum)	**FV**	144	95.4	10.3	100.0	106.7	0.349	0.727	-0.1
	TAU	159	95.5	8.1	100.0	66.4			
Tooth pain	**FV**	144	91.7	16.5	100.0	271.0	0.169	0.866	0.8
	TAU	159	90.9	17.9	100.0	319.8			
Tooth pain when eating / drinking	**FV**	144	95.0	12.4	100.0	153.7	0.129	0.897	0.5
	TAU	159	94.5	13.4	100.0	179.2			
Dark coloured teeth	**FV**	144	96.7	14.3	100.0	203.2	0.932	0.351	1.4
	TAU	159	95.3	16.2	100.0	262.4			
Gum pain	**FV**	144	96.0	13.8	100.0	189.4	-0.935	0.350	-1.9
	TAU	159	98.0	7.4	100.0	55.1			
Bleeding when toothbrushing	**FV**	144	97.6	11.2	100.0	125.2	-0.497	0.619	-1.2
	TAU	159	98.7	5.5	100.0	30.1			
SOHO-5									
SOHO Total (sum)	**FV**	147	0.3	0.8	0.0	0.6	-0.689	0.491	-0.1
	TAU	159	0.4	1.1	0.0	1.2			
Difficulty eating	**FV**	147	0.2	0.5	0.0	0.2	-0.667	0.505	-0.1
	TAU	159	0.3	0.6	0.0	0.4			
Difficulty speaking	**FV**	147	0.0	0.2	0.0	0.0	1.394	0.163	0.0
	TAU	159	0.0	0.2	0.0	0.0			
Difficulty playing	**FV**	147	0.0	0.1	0.0	0.0	-0.512	0.609	0.0
	TAU	159	0.0	0.2	0.0	0.0			
Avoiding smiling (appearance)	**FV**	146	0.0	0.2	0.0	0.0	-0.350	0.727	0.0
	TAU	158	0.0	0.1	0.0	0.0			
Avoiding smiling (state of teeth)	**FV**	147	0.0	0.0	0.0	0.0	-0.955	0.340	0.0
	TAU	159	0.0	0.1	0.0	0.0			
Difficulty sleeping	**FV**	147	0.0	0.1	0.0	0.0	-0.906	0.365	0.0
	TAU	159	0.0	0.4	0.0	0.1			
Self-confidence affected	**FV**	147	0.0	0.2	0.0	0.0	-0.599	0.550	0.0
	TAU	158	0.0	0.2	0.0	0.0			

Notes: WMW - Wilcoxon Mann-Whiney U-test (also known as Wilcoxon rank-sum test). * Two-sided p-value. PedsQL-OH: The higher the 0-100 scale score, the better is the quality of life. SOHO-5: The lower the score, the better is the quality of life.

6.11 Discussion

Previous research indicated that the universal nursery toothbrushing component of Childsmile was both clinically effective (Macpherson et al. 2013) and highly cost-saving, as well as being most cost-saving in the most deprived populations (Anopa et al. 2015). The estimated savings ranged from £1m to £5m per year. In the eighth year of the toothbrushing programme the expected savings were more than two and a half times the costs of the programme implementation. Leading on from this, however, there were doubts with regard to the cost-effectiveness of the add-on nursery FV component. This was tested within the PT@3 trial.

The aim of the economic evaluation (EE) of the PT@3 trial was to assess the cost-effectiveness of preventive FV in the context of the Childsmile programme. Namely, to estimate the cost-effectiveness of the FV (plus TAU) intervention compared with TAU only (control) in three ways: by using CUA, with the outcome being quality adjusted life year (QALY); CEA with oral health improvement or worsening, as measured by the d3mft as an outcome; and CCA, which covered several available outcome measures: the CUA and CEA results, as well as other general health and oral health-related quality of life (GHQoL and OHQoL) measures.

The current chapter presented the results of the EE of PT@3 Study based on a 534-participant sample (N_{FV} = 265; N_{TAU} = 269). Overall, the results indicated that, within the context of nursery/preschool setting and under the PT@3 trial conditions, the total mean cost per participant for the intervention (FV plus TAU) was greater than the comparator (TAU only). This result was persistent in all sensitivity scenarios. However, in all scenarios the difference was not statistically significant. No statistically significant or clinically meaningful differences were found across the primary (worsening of d3mft) and secondary outcomes (including QALY gained and various GH/OHQoL measures).

The CEAC for the CUA showed that there would be an 11% probability of the FV intervention being cost-effective at a NICE societal willingness to pay threshold of £20,000 per additional QALY (base-case scenario), while in sensitivity analysis

scenarios the probability of the intervention being cost effective ranged from 9% to 20%.

6.11.1 Comparison of PT@3 results with other economic evaluation studies on fluoride varnish

Two previous studies on the cost-effectiveness of fluoride varnish (FV) in preschoolers or younger children were identified (Tickle et al. 2016, O'Neill et al. 2017, Anderson et al. 2019) as well as one cost analysis study (Buckingham and John 2017), and one trial conducted in older children, aged 6-7 years, which included both a CEA and a CUA (Chestnutt et al. 2017). These studies varied in their settings and the comparator interventions. Further details on each of these studies are described below.

A two-arm parallel-group randomized controlled trial (Northern Ireland Caries Prevention in Practice (NIC-PIP)) (Tickle et al. 2016, O'Neill et al. 2017) measured the cost-effectiveness of caries prevention in caries-free children aged 2-3 years at baseline attending 22 general dental practices. The intervention was a combination of fluoride varnish, free toothbrush and fluoride toothpaste, and standardized prevention advice, while the control was prevention advice only. Interventions in both study groups were provided at 6-monthly intervals during a 3-year follow-up. The study found statistically significant mean difference in direct health care costs between the groups of £107.53 (£155.74 intervention, £48.21 control, $P < 0.05$) per child. When all health care costs were compared, the intervention group's mean cost was £212.56 more than the control group (£987.53 intervention, £774.97 control, $P < 0.05$). By comparison, the results of the PT@3 study showed that the difference in total cost was not statistically significant: the FV intervention had an incremental cost of £68.37 in comparison with TAU only (£665.90 intervention, £597.52 control, $p = 0.38$). In the PT@3 study total costs included: a) participant healthcare (NHS) resource use; b) family costs (representing societal costs), which comprised of time away from work / usual activities due to child's ill health; and, for the FV group only, c) intervention costs.

In the NIC-PIP trial, statistically significant differences in outcomes were only detected with respect to carious surfaces (but not for the proportion of children

who remained caries-free, nor for the number of episodes of pain), while in PT@3 the difference in the incremental d3mft change between the groups was found to be not statistically significant, with a wide 95% confidence interval (the difference in difference of 0.071, 95% CI -0.237, 0.406, p = 0.67).

A Swedish trial aimed to economically evaluate an enhanced caries-preventive programme “Stop Caries Stockholm” (SCS) in comparison with the standard preventive programme in children aged one to three years (Anderson et al. 2019). This trial was similar to the PT@3 Study in the way that their standard programme already comprised of many preventive efforts, and the additional intervention was the fluoride varnish and a higher frequency of the other interventions (6-monthly, versus 12-monthly). The standard programme (comparator) in Anderson and colleagues’ study included toothbrushing instructions to the parents, information about toothbrushing, dietary counselling and a toothbrush and fluoride toothpaste pack free of charge. The standard interventions were delivered on a 12-monthly basis. The test intervention (the SCS programme) incorporated all of the components of the standard programme, but additionally, the children in the intervention group received FV treatments every six months, in conjunction with standard intervention. At age 36 months, no significant difference in caries prevalence of defs (decayed, extracted, filled tooth surfaces) had occurred between the test and the reference groups. It was found that the SCS intervention was more costly, with total societal costs of EUR 139.58 for the intervention group and EUR 96.69 for the comparator (total dental health care costs of EUR 96.08 intervention and EUR 70.12 comparator). No p-values or confidence intervals were reported in that paper. These SCS trial total costs were substantially lower that the total costs in the PT@3 Study. However, the results of these two trials cannot be compared directly, due to substantial differences in the child ages (1-3-year-olds in the SCS trial compared to 3-5-year-olds in PT@3), differences in the intervention and comparators and the methods used to conduct the economic evaluations (a bottom-up data collection was used in the PT@3 Study, whereas the SCS trial used a large number of assumptions, including those based on previous research).

An English study investigated the feasibility and costs of a pilot oral health improvement programme for children aged 3-7 years, which included FV

applications in school and preschool settings (Buckingham and John 2017). The children were attending preschools and primary schools in four pilot sites within areas of deprivation and areas with relatively high levels of dental decay. The intervention included daily supervised toothbrushing in the schools; oral health education provided for children, parents and school staff to encourage toothbrushing at home, improve diet and visit a dentist regularly; parents of children who needed treatment were sent letters signposting them to local dental practices; and three applications of FV per year were offered. The programme costs included: staff costs, non-pay costs and the delivery of FVA. The results of the study showed that the percentage of children with dental decay experience went up in all study areas except for one site, where it stayed at the same level. There were larger dental decay increases in the cohorts with older children. A positive outcome was an increase in the number of children who were reported by their parents as having had at least one dental visit by the end of the pilots. The mean total cost of delivering the programme was £71 per child. By comparison, in the PT@3 Study, the mean intervention cost per child in the FV group was £32.66 (SD £13.21). However, the PT@3 intervention costs only included staff labour and travel costs and consumables and equipment related to the delivery of FVAs, whereas the intervention in the Buckingham and John (2017) study was more complex and included more components.

A study conducted in Wales involved children aged 6-7 years and compared the clinical effectiveness and cost-effectiveness of fissure sealants (FS) and FV in preventing dental caries in first permanent molars (Chestnutt et al. 2017). The interventions were delivered in mobile dental clinics in primary schools located in areas of high deprivation. It was found that FV was less costly than fissure sealants, with similar outcomes achieved (the numerical differences in outcomes were not statistically significant). The intervention cost per child over the course of the trial was £64.16 for FV and £74.12 for FS (whereas in the PT@3 Study, the mean intervention cost per child in the FV group was £32.66). The total costs of the two technologies showed a small but statistically significant difference. The mean cost to the NHS per child was £500 for FS, compared with £432 for FV, that is a difference of £68.13, (95% CI £5.63, £130.63; p = 0.033), in favour of FV. The Chestnutt and colleagues' FV mean cost was lower than the FV mean cost per child in the PT@3 study (£665.90). However, it was not possible to

meaningfully compare the mean total cost per child in a FV arm in the Chestnutt and colleagues' study or in the other identified studies, with the PT@3 mean costs due to the differences in the EE perspectives used, the methods used to evaluate and calculate the costs (for example, a trial-based cost data collection compared to assumptions based on previously published information), and the differences in the studies' settings.

6.11.2 Discussion on the cost-utility and cost-effectiveness analyses results

Over the 24-month follow-up the intervention (FV plus TAU) was more costly while generating marginally less QALYs, than the control arm (TAU only). However, these differences were not statistically significant for both costs and QALYs. FV acquired 1.859 QALY (95%CI 1.849, 1.878), while TAU acquired 1.863 (95%CI 1.844, 1.874), the difference of -0.004 (95%CI -0.016, 0.007, p=0.64). The average total cost per participant was £665.90 (95%CI £564.38, £752.84) in the FV group and £597.52 (95%CI £519.29, £674.27) in the control group. These total costs included: (a) Participant healthcare (NHS) resource use; (b) Family costs (representing societal costs), which included time away from work / usual activities due to child's ill health; and, for the FV group only, (c) Intervention costs including staff labour, staff travel, and materials costs. The intervention group had an incremental cost of £68.37 (95%CI -£18.04, £143.82) greater than the control group (p = 0.38). The mean intervention cost per child in the FV group over the course of the study was £32.66 (SD £13.21).

Only one oral health study in preschoolers that used a cost-utility analysis (CUA) and employed the CHU9D instrument was identified (Koh et al. 2015). It was a model-based study (not an RCT), which aimed to evaluate the cost-effectiveness of a home-visit intervention conducted by oral health therapists relative to a telephone-based alternative and no intervention. A Markov model was built to combine data on dental caries incidence, dental treatments, quality of life and costs for a cohort of children from age 6 months to 6 years. The outcome measures were costs, QALYs and the number of carious teeth prevented. The CHU9D questionnaire was distributed to a consecutive subsample of 100 parents who presented to the community paediatric dental clinic with their children

aged 5 years and younger with caries. The mean utility score for the "caries" health state was 0.90 (SD = 0.12) with a range of 0.38 to 1.00. Utility values were smaller in children with greater numbers of carious teeth: children who had <5 carious or filled teeth had a mean utility value of 0.91 compared to 0.88 for children with more than five carious/filled teeth. By comparison, in the PT@3 Study the utility values by study arm were in the range from 0.937 to 0.944 at various points in time during the study. Lower utility values, i.e. worse quality of life, in the Koh and colleagues' study (Koh et al. 2015) can be explained by the fact that their utilities were derived from children with early childhood caries requiring treatment at a dental clinic, whereas the PT@3 participants in both intervention groups included children with and without caries from the general population.

The results of the probabilistic sensitivity analysis in the PT@3 Study indicated that the vast majority of the simulated 1,000 cost-utility dyads are above the X-axis, meaning that the intervention (FV) was more expensive comparted to the control (TAU). Likewise, the majority of the simulated cost-utility dyads are to the left of the Y-axis, indicating that the intervention was unlikely to improve quality of life outcomes. The fact that the majority of the dyads are situated in the north-west quadrant means that in the majority of the bootstrap iterations TAU dominates: namely, the FV intervention is less effective (in terms of QALY gained) and more costly than TAU.

In all PT@3 sensitivity analyses scenarios, the intervention was more costly and gained less QALYs than the control. Similarly, in all scenarios the probability of the intervention being cost effective (at the £20,000/QALY gained threshold) was low ranging from 9% to 20%.

With regards to the CEA results of the PT@3 Study, the d3mft effectiveness data were analysed using a "difference in difference" approach. The "d3mft difference" was used as an outcome, which for each child in each study group was the difference between their d3mft at 24-months minus their d3mft at 0-months. The mean d3mft difference was higher in the intervention group, in comparison with the TAU group, indicating that on average the intervention arm children had a slightly greater worsening of the d3mft. The difference in

difference between the groups was 0.071, although it was not statistically significant (p = 0.67) with a wide 95% confidence interval (-0.237, 0.406).

The results of the probabilistic sensitivity analysis with the d3mft difference in difference as an effectiveness measure showed that in the majority (66%) of the 1,000 bootstrap simulations the intervention was more costly and less effective while in 29% the intervention was more costly and more effective.

Taking in account the non-significant results of the primary endpoint analysis in the overall PT@3 Study (27% of children in the FV group had a worsening of d3mft versus 32% of the TAU group children; OR=0.80, 95%CI 0.62, 1.03, p = 0.078) (McMahon et al. 2020), it can be suggested that FV in nursery settings in addition to all other routine components of Childsmile (TAU) is neither effective enough nor cost-effective.

6.11.3 Discussion on the cost-consequence analysis results

The results of the cost-consequence analysis (CCA) indicated that none of the cost or outcome differences between the two groups, FV and TAU, were statistically significant. In the base-case scenario, the mean total cost per child in the intervention group (which included intervention cost and participants' NHS resource use costs) was £68.37 higher than in the control group. When "other" NHS resources costs were added to the total cost this difference reduced to £54.98.

With regard to OH/GHQoL, the mean differences between the groups showed that the children in the FV group had marginally worse OH/GHQoL at 24 months (although the differences were not statistically significant). The exception was the PedsQL school/nursery domain score where the difference was positive (but non-significant), indicating that the FV children performed somewhat better with regards to this domain.

6.11.3.1 PedsQL Core

The PedsQL Core scores study group means (the total score, by-domain and by-item scores) were not significantly different apart from one item where the p-

value was approaching significance – “Other children not playing with him/her” (p = 0.052).

Only one previous UK-based study that used the parent-rated toddler version of the PedsQL Core was identified. The study aimed to assess its psychometric properties in healthy UK toddlers and included 256 parents of healthy 2–4-year-olds (Buck 2012). The mean scores were as follows: Total score 87.8; Physical Health 92.6; Emotional Functioning 76.0; Social Functioning 89.9; Nursery Functioning 92.3; and Psychosocial Summary 84.6. The author concluded that the toddler version of the PedsQL performed well in a UK sample, apart from the Nursery Functioning scale. The PT@3 mean PedsQL scores were comparable to the abovementioned results. In PT@3, at the end of the study, the mean Total scores were 88.2 (FV) and 88.7 (TAU), Physical Health: 92.1 and 92.4; Emotional Functioning: 79.8 and 80.0; Social Functioning: 88.6 and 90.7; Nursery Functioning: 90.6 and 90.2; and Psychosocial Summary: 85.7 and 86.5, respectively. Overall, it seems that the PT@3 participants were representative of generally healthy toddlers/pre-schoolers in the UK, as PedsQL Core scores in the PT@3 trial were similar to the Buck’s study (2012), and that caries in those children with d3mft>0 did not substantially affect their GHQoL.

6.11.3.2 CHU9D

There was almost no difference between the PT@3 study groups’ means for the CHU9D scores at the end of the study. All differences in CHU9D means by item were within the range from -0.05 to 0.11, which is low taking in account that the full scale for each item is 1 to 5. None of these differences were statistically significant. In the available case analysis, the mean utility at the 24-months data collection point in the FV group was 0.942 (SD=0.065) and 0.946 (SD=0.062) in the TAU group, with a p-value of 0.64, meaning the was no significant difference in utility between the groups.

The mean CHU9D utility indices in the PT@3 Study at 0, 12 and 24 months were found to be higher than in several studies that included older children. In the PT@3 multiple-imputed dataset, the baseline utility was almost the same for the two groups (0.938 for FV and 0.937 for TAU), the utility values at 12 months

were 0.941 (FV) and 0.944 (TAU), while the utility values at 24 months were 0.939 for FV and 0.943 for TAU. At each point in time the utility differences between the two groups were not statistically significant.

In comparison, in a UK-based study of 5-6-year-old children the mean CHU9D indices were 0.826 for males and 0.824 for females (Frew et al. 2015). In another British study of 6-7-year-olds the CHU9D index was 0.86 (Canaway and Frew 2013). In a New Zealand study the mean CHU9D index was 0.87 for the 6-7-year-old subgroup (Foster Page et al. 2014), while in another New Zealand-based study involving 6-9-year-olds the mean CHU9D values were 0.88 at baseline and 0.90 at a 1-year follow-up (Foster Page et al. 2015). The PT@3 utility values were most similar to a Welsh study "Seal or Varnish" that compared the cost-effectiveness of fissure sealants (FS) and FV in children aged 6-7 years (Chestnutt et al. 2017), however the PT@3 values were still somewhat higher. In the Chestnutt and colleagues' study the mean utility values at each of the follow-up points were similar for both interventions (the differences were not statistically significant). In the FS group, the mean utility value was in the range 0.926 to 0.933 at various time points throughout the study, while in the FV group the range was 0.928 to 0.933. However, of note is the fact that all the above-mentioned comparator studies used a child self-report version of the CHU9D, rather than a parental proxy report on the child that was used in the PT@3 trial.

Previous studies showed that CHU9D was unresponsive to the caries index change following a dental treatment (Foster Page et al. 2015) and did not differentiate between children of various body weight categories (Frew et al. 2015). There were no statistically significant associations observed between caries status and the CHU9D in a New Zealand study, which included 6-9-year-old children receiving dental care (Foster Page et al. 2015). The CHU9D was found to be unresponsive to the changing components of the dmfs+DMFS index score (a dental effectiveness score, which is the number of decayed, missing due to decay, and filled tooth surfaces in both the deciduous and permanent dentition). The authors concluded that CHU9D might not be sensitive enough to be used as an outcome measure in economic evaluation in the area of paediatric dentistry.

The conclusions of Foster Page and colleagues (2015) together with the results of this PT@3 EE, which showed that there was no statistically significant differences between the trial arms neither in the QALYs accumulated over the two years of the trial, nor in the overall CHU9D score at the 24-months, or CHU9D scores by item, poses the question: “Is the CHU9D sensitive enough to be meaningfully used in EEs of oral health interventions aimed at younger children?” Further research of the instrument’s psychometric properties and more longitudinal preschooler child oral health studies using CHU9D is recommended. Moreover, the development and testing of an oral health- or caries specific preference-based instrument specifically aimed at preschoolers / their proxies can be suggested. An example of this, for slightly older children, is the ongoing work of Dr Helen Rogers and colleagues on turning CARIES-QC into a caries-specific preference-based measure (Rogers et al. 2020). Disease-specific quality of life instruments tend to be more sensitive to the changes related to the condition (responsiveness to change) (Drummond 2001) and may describe the functioning of a subject with greater clarity than a generic instrument.

A UK-based study aimed to explore the association between weight status and GHQoL in 5-6-year-old children found that the GHQoL of children who were overweight or obese was not statistically significantly different from children who were healthy or underweight (Frew et al. 2015). This result was the same for both GHQoL measures used: the CHU9D (a preference-based instrument) and PedsQL (a non-preference-based instrument), the same GHQoL measures that were used in the PT@3 Study. The mean CHU9D and PedsQL scores for males were 0.826 and 71.10, respectively, and for females they were 0.824 and 69.72. In PT@3 both mean CHU9D and PedsQL scores were found to be higher: the CHU9D range was 0.937 to 0.944 and PedsQL total scores were between 88.2 and 88.7. The results of the study by Frew and colleagues (2015) as well as the PT@3 trial results indicate that in young chid populations both the CHU9D and PedsQL Core instruments might not be sensitive enough to excessive body weight or the presence of dental caries.

6.11.3.3 PedsQL-OH

With regards to the OHQoL measures used in the PT@3 Study, small non-significant differences in the PedsQL-OH means by item and for the total OH score (range: from -1.9 to 1.4) between the two intervention groups were found.

Only one previously published study that used the PedsQL-OH toddler version in a preschool population was identified. All other identified papers reported on studies that used PedsQL-OH in mixed-age child populations. The aim of a recently published study was to cross-culturally adapt the parent-reported PedsQL-OH toddler version into Spanish and to assess the acceptability, reliability and validity of this version in a Chilean preschool population (Atala-Acevedo et al. 2020). This cross-sectional study was carried out in public preschools in children aged 2-5 years and their parents. The majority of the participating families (76%) had a low socioeconomic status, and 54% of the children in the study had caries. The mean PedsQL-OH score in the Chilean study was 89.1 (SD=16.1), with a median of 95. The median for the subgroup of children without caries (dmft = 0) was 100.0 while for those with caries (dmft >= 1) it was 90.0. In comparison, in the PT@3 Study the mean PedsQL-OH scores were 95.4 (SD=10.3) for the FV group and 95.5 (SD=8.1) for the TAU group, while the medians for both groups were 100.0.

In the original PedsQL-OH development and validation study conducted in the USA, the mean parental-proxy score was 88.68 (SD=15.82) (Steele et al. 2009). The participants in that study were families with children between the ages of 2-18 years who attended for scheduled dental visits in an outpatient dental clinic. A Brazilian study, which aimed to evaluate the psychometric properties of the Portuguese version for Brazilian translation of the PedsQL-OH, was conducted with children and adolescents aged 2-18-years and their parents who were selected from the general population (Bendo et al. 2012). The overall study population mean parental-proxy PedsQL-OH score was 87.15 (SD=14.71), while the score for caries-free children was 90.6 (SD=11.5) and it was 81.6 (SD=15.9) for those with caries. In the PT@3 trial the mean PedsQL-OH scores were 95.4 (FV group) and 95.5 (TAU group), which were higher than the Bendo and colleagues' mean score for caries-free children. This could be explained by the

fact that the children in PT@3 Study were substantially younger and were less likely to exhibit any oral health problems (not necessarily related to the presence or absence of caries). A study with an objective to translate and evaluate the psychometric properties of the Iranian version of the PedsQL-OH conducted in children aged 8–18 years and their parents resulted in an even lower mean parental-proxy score of 74.82 (SD=26.1) (Pakpour et al. 2011).

6.11.3.4 SOHO-5

With regards to the SOHO-5 questionnaire, the means for both groups equalled zero for almost all items, apart from "Difficulty eating" (Mean $_{FV}$ = 0.2, Mean $_{TAU}$ = 0.3; p = 0.51). The medians for both groups for all items and the total score equalled zero. The SOHO-5 total mean score was 0.3 for the FV group and 0.4 for the TAU group (p = 0.49).

A previous study, which aimed to develop and assess the reliability and validity of SOHO-5 in the UK, was conducted on a sample of 5-year-olds and their parents in the NHS Greater Glasgow and Clyde area in Scotland (Tsakos 2010, Tsakos et al. 2012). Parental-proxy SOHO-5 scores were sourced from an unpublished report (Tsakos 2010). The range of SOHO-5 total mean scores for the subgroups without dental problems were in the range from 0.39 to 0.52, while for the subgroups with dental problems the range was 0.72-1.44, with higher scores indicating worse OHQoL. In comparison, in the PT@3 study the mean scores at 24-months were 0.3 (SD=0.8) in the FV group and 0.4 (SD=1.1) in the TAU group. These means are comparable with the means for the subgroups of children without dental problems from the Tsakos' report.

SOHO-5 scores in the PT@3 Study were substantially lower (indicating better OHQoL) than those in two studies conducted on children seeking treatment at dental practices (Abanto et al. 2013a, BaniHani et al. 2018).

6.11.4 Interpretation of PT@3 results in context of previous research

Overall, taking into account the results of the PT@3 economic evaluation, in conjunction with the proven effectiveness (Macpherson et al. 2013) and cost-

saving (Anopa et al. 2015) generated by the whole-Scotland universal nursery toothbrushing programme, as well as with the results of a recent Childsmile data linkage study (Kidd 2019), which showed that children who were participating in nursery toothbrushing had reduced odds of caries experience relative to children who were not participating in nursery toothbrushing, it seems that the continuation of the targeted nursery FV programme in its current (pre-COVID-19) form and shape in addition to nursery toothbrushing would not be deemed a worthwhile use of scarce health care resources in relation to the health benefits to be gained through investment of proven cost-effective interventions. Moreover, the same Childsmile data linkage study indicated that nursery FV applications were not independently associated with caries experience. Children targeted for nursery FV, in comparison to children receiving zero applications, had no reduction in the odds of caries experience regardless of the number of FV applied (in case of five FV applications *vs* no applications: OR=0.97; 95%CI 0.89, 1.06) (Kidd 2019).

6.12 Strengths and limitations

This EE has been undertaken as part of a rigorous randomised trial to assess the clinical effectiveness and cost-effectiveness of FV plus TAU and TAU only delivered in nursery/preschool settings. Data were collected prospectively alongside the trial. This approach allowed for a more precise estimation of both costs and outcomes, in comparison with, for example, using assumptions and/or previously published information. A further strength of the PT@3 economic evaluation (EE) was that a bottom-up approach was used in the data collection and calculation of costs and outcomes. Another strength is that multiple outcomes were measured in the PT@3 Study. These included clinical outcomes (based on d3mft and d3mfs indices) and several quality of life measures: a preference-based GHQoL measure (which allowed to calculate QALYs), a widely used non-preference-based GHQoL measure and two OHQoL measures. The QALY outcomes allow for the PT@3 intervention to be compared to any other intervention that was evaluated using CUA, both within the oral health area and broader, while the other GH/OHQoL measures allowed to assess the influence of the intervention and the comparator on various aspects of the child's quality of life.

There are a number of limitations of the EE of the PT@3 Study. Firstly, the EE was conducted on a sample of the full trial (534 participants in total), which did not allow for meaningful subgroup analyses, as had been planned *a priori*. Secondly, the time horizon was the duration of the PT@3 trial, namely, 24 months. Hence the EE results do not reflect outcomes throughout later childhood or over the whole life course. It would be useful to construct, for example, a longer-term Markov model, but this was outside the remit of the current thesis. There is also a limitation of the available GHQoL or OHQoL questionnaires: currently there is no preference-based instrument that would be sensitive enough to be used in CUAs in paediatric oral health research.

6.13 Conclusions

The findings of this trial demonstrate that there was no statistically significant difference in total costs, QALYs accumulated, and in several GHQoL and OHQoL measures at 24 months (CHU9D utility, PedsQL, PedsQL-OH and SOHO-5 scores) between the two groups. There was no statistically significant difference in new caries development between the two groups. The results show that applying FV in nursery settings in addition to the existing TAU (which was all other components of the Childsmile programme, apart from nursery FV) is not cost-effective.

In view of previously proven clinical effectiveness and economic worthiness of the universal nursery toothbrushing component of Childsmile, which was shown to be highly cost-saving, as well as being most effective and cost saving in most deprived populations, it seems that the continuation of the targeted nursery FV programme in its most recent (pre-COVID-19) form and shape in addition to nursery toothbrushing and other routine Childsmile components is not advisable. In summary, there is no economic evidence to justify the continued investment in the FV programme in relation to the health benefits to be gained through investment of proven cost-effective interventions. The findings of this EE should be used to inform the future Childsmile strategic policy development.

Chapter 7 Discussion, recommendations and conclusions

7.1 Introduction to Chapter 7

Early childhood caries (ECC) continues to be a pandemic disease and a public health problem worldwide (WHO 2017b) and is more prevalent among the more socially disadvantaged groups (Edelstein 2006, Anil and Anand 2017). ECC can have a major impact on children's health and quality of life as well as represent cost to society (Tinanoff et al. 2019). Research indicates that children who develop caries in early childhood are likely to have a high risk of the disease in adolescence and adulthood, in permanent teeth (Li and Wang 2002, Anil and Anand 2017, Hall-Scullin et al. 2017, Seow 2018, Tinanoff et al. 2019). Dental caries is a preventable disease and currently a range of nationwide programmes, such as Childsmile in Scotland (Childsmile 2020b) and Designed to Smile in Wales (Designed to Smile 2020), community-based programmes and clinical strategies exist to reduce caries prevalence in children (Rogers et al. 2020).

ECC poses an economic burden to individuals, the health sector and society more broadly (Phantumvanit et al. 2018). However, it has been shown that oral health interventions in early childhood can be a cost-effective measure to prevent caries (Anopa et al. 2015, Public Health England 2016c, York Health Economics Consortium 2016e).

The aim of this doctoral research was to explore the role of economic evaluation in primary caries prevention in preschool children aged 2-5 years. This aim was met through answering the following three research questions.

1) What is the existing evidence in the field of economic evaluation of primary caries prevention in children aged 2-5 years?

2) Which general health and oral health-related quality of life measures (both parental proxy and child self-report) have been used in 3-5-year-old populations? And which of these measures are best suited to be used in the Protecting Teeth @ 3 randomised controlled trial?

3) Is the application of fluoride varnish delivered in nursery settings in addition to the other usual Childsmile components (treatment as usual) cost-effective in comparison with treatment as usual only?

Consequently, this thesis addressed these questions through three empirical work segments:

1) A systematic review of economic evaluations of primary caries prevention in 2-5-year-old preschool children (presented in Chapter 3).

2) A non-systematic review of instruments for measuring general and oral health-related quality of life in 3-5-year-old children (Chapter 4).

3) An economic evaluation of the Protecting Teeth @ 3 randomised controlled trial (Chapters 5 and 6).

This chapter will outline the key findings from these three pieces of empirical work, provide an overall discussion of the results and explore the strengths and limitations of this research. Implications of this research for policy making as well as implications and recommendations for future research will be explored. Finally, overall conclusions will be provided.

The next section will discuss the key findings from each segment of the study.

7.2 Key findings

The main findings of this thesis were as follows:

i. The results of the systematic review in Chapter 3 indicated that although the number of economic evaluations studies relating to primary caries prevention interventions in children aged 2-5 years has been increasing in recent years, a number of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist items were inadequately reported in a substantial proportion of the reviewed studies. The systematic review has highlighted wide variation in the following areas: a) types of caries

prevention interventions investigated; b) effectiveness measures used; c) how costs and outcomes are reported; and d) study perspective (when indicated).

ii. The methodological limitations of available studies, identified in the Chapter 3 review, preclude meaningful comparisons across studies as well as compromise the evidence base for strategies in relation to caries prevention in 2-5-year-olds. Due to small numbers of studies investigating each intervention type (for example, fluoride varnish, oral health education, dental sealants, toothbrushing, fluoridated food and drinks, water fluoridation) and the low methodological quality of many of the reviewed economic evaluations, it was not possible to arrive at reliable conclusions with regards to the economic value of primary caries prevention.

iii. There is a lack of use of preference-based outcome measures in the field of caries prevention for young children. The systematic review in Chapter 3 identified only one study, which employed cost-utility analysis using a preference-based outcome measure. This likely reflects the challenges with conducting economic evaluations in this young age group, the availability of suitable preference-based measures for this age group, and also flags up the limitations with the use of existing economic evaluation studies for the purposes of decision making in dental healthcare.

iv. The review of general health and oral health-related quality of life (GHQoL and OHQoL) measures, presented in Chapter 4, identified a range of existing questionnaires for use in preschool populations (age 3-5 years). Their strengths and limitations were considered in relation to applying them in the Protecting Teeth @ 3 Study, a preschoolers' oral health randomised controlled trial. Four instruments were selected to be used in the trial: the CHU9D (a preference-based HRQoL measure), PedsQL Core (a non-preference-based HRQoL measure, which is often used as a "gold standard"), PedsQL-OH (a short oral health specific add-on to PedsQL Core) and SOHO-5 (an oral health specific measure). The results of the review can assist researchers and evaluators of preschool oral health

improvement programmes in understanding the differences between the included GHQoL and OHQoL measures and to help them in choosing the best-suited instrument(s) for their projects.

v. The Chapter 4 review identified only two preference-based general health-related quality of life instruments that were used in children under six years of age: one interviewer-administered (QWB), and the other parental self-administered (CHU9D). Even then, the CHU9D was originally developed with children aged 7-11 years, rather than with preschool children; while QWB is applicable to a wide age range from 4 to 18 years (it is not preschooler specific). No preference-based oral health-related quality of life measures for preschoolers were identified. Further research and development of new preference-based measures suitable for preschoolers, or their parents/guardians as a proxy, are required. Due to the young age of preschool children and their inability to self-report, it can be recommended to focus future research efforts on the development of suitable preference-based instruments designed specifically for proxies (parents/guardians).

vi. The findings of the Protecting Teeth @ 3 trial economic evaluation (Chapter 6) demonstrate that there was no statistically significant difference in total costs, QALYs accumulated, the change in d3mft, and in several GHQoL and OHQoL measures at 24 months (CHU9D utility, PedsQL, PedsQL-OH and SOHO-5 scores) between the intervention and control groups. The results show that applying fluoride varnish in nursery settings in addition to the existing treatment as usual (which was all other components of the Childsmile programme, apart from fluoride varnish applied in nursey settings) is not cost-effective. The findings of this economic evaluation will be used to inform future Childsmile strategic policy development.

7.3 Discussion

7.3.1 Systematic review of economic evaluations of primary caries prevention in 2-5-year-old children (Chapter 3)

The specific objectives of Chapter 3 were: a) To describe and summarise currently available scientific literature on economic evaluations (EEs) of primary caries prevention in preschool children aged two to five years; and b) To evaluate the reporting quality of the included full EE studies, using a quality assessment tool developed for appraisal of EEs.

This is the first systematic review to focus on the EEs of oral health improvement interventions targeted at the early life. This period has been shown to be crucial in influencing health in later years (Colak et al. 2013, ICOHIRP 2015), and early intervention is also likely to provide significant long term returns to early investment (Heckman 2008, Cunha and Heckman 2010, Scottish Government 2010a, Heckman 2011).

The proportion of full EEs increased over time, especially from 2000 onwards. The most widely used type of analysis were cost analysis and CEA, which is similar to the findings of a recent systematic review of EEs in wider child oral health research (Rogers et al. 2019). A significant proportion of the papers did not state the perspective used in the analysis: 83% of partial EEs and 44% of all full EEs, similar to the results of a previous systematic review of CUAs of oral health interventions (Hettiarachchi et al. 2018).

The review identified 16 full EEs, which used a variety of oral health and economic outcome measures. This variation makes it challenging to compare the cost-effectiveness of individual caries prevention interventions. This concurs with the conclusions of two previous systematic reviews (Hettiarachchi et al. 2018, Rogers et al. 2019). Interpretation of cost-effectiveness ratios for dental health outcomes is similar to the standard challenges of using CEA when comparing different outcomes. Without the use of an accepted threshold for a generic outcome, such as a QALY, comparability is not possible. Only one study (Koh et al. 2015) used a preference-based health-related quality of life measure that allows calculation of QALY as one of the outcomes, which, in turn, allows a

comparison of cost-utility results of various interventions' evaluations. This lack of evidence reveals a clear gap in relation to preschoolers' oral health research.

While over 40% of the reviewed full EE papers concluded in favour of the intervention(s) under investigation, there were small numbers of studies investigating each intervention type (for example, fluoride varnish, oral health education, dental sealants, toothbrushing, fluoridated food and drinks, water fluoridation). The studies were underpowered, used simple spreadsheet-based calculations, or were pilot studies, making it challenging to draw reliable conclusions with regard to the value of primary caries prevention. There was only one full EE conducted alongside a well powered randomised controlled trial, which was deemed to be of high reporting quality (O'Neill et al. 2017).

The results of the quality assessment of the full EEs, using the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist (Husereau et al. 2013, Frederix 2019), showed substantial variation in reporting quality. It was found that more recent papers were of higher reporting quality than earlier ones, which could be explained by the development of EE reporting standards within the last 20 years (Drummond and Jefferson 1996, Siegel et al. 1996, Evers et al. 2005, Philips et al. 2006, Husereau et al. 2013b).

The lack of high-quality EEs makes it difficult for decision-makers to determine which interventions to provide within the remit of health services and local authorities. Within child oral health research, this paucity of EEs could be explained firstly by the fact that oral health is often seen as a separate entity to general health (Haber et al. 2015, Doshi and Patel 2017) and hence receives lower priority, especially with regards to health economics research. Secondly, there is a lack of a suitable instrument to measure QALYs in preschool populations. At present, only one generic preference-based measure has been used in child oral health research - the Child Health Utility 9 Dimensions (CHU9D), in two studies (Foster Page et al. 2014, Foster Page et al. 2015). CHU9D was shown not to be sensitive enough to be used as an outcome measure in EEs (Foster Page et al. 2015). Moreover, CHU9D was originally developed with and for older children, aged 7-11 years, rather than for use in preschool children (or their proxies). This poses the question as to whether the CHU9D can be

meaningfully used in CUAs and in wider oral health research in younger children. Further exploration of the instrument's psychometric properties and more oral health intervention studies using CHU9D in preschoolers can be recommended. In addition, development and testing of an oral health- or caries specific preference-based instrument specifically aimed at preschoolers and/or their proxies can be suggested. Thirdly, as conducting research, including EEs, on/with young children is overall challenging (Scott 2000), it can be specifically recommended to develop suitable preference-based instruments designed for proxies, rather than preschool children themselves.

Similar to the results of the present systematic review, a recent scoping review of studies on cost-effectiveness of school-based interventions for caries prevention (i.e. studies on older children and adolescents) (Amilani et al. 2020) has found that the disease-specific outcome measures differed across the studies which impeded comparisons of cost-effectiveness between interventions and settings. Moreover, Amilani and colleagues found that none of the included studies reported on QALYs. On a positive note, they identified an increasing trend in publication of cost-effectiveness studies of school-based dental caries preventive interventions.

7.3.2 Instruments for measuring general and oral health-related quality of life in 3-5-year-old children (Chapter 4)

The main research questions for the general health and oral health-related quality of life (GHQoL and OHQoL, respectively) instruments review were: a) What are the existing GHQoL and OHQoL instruments for the age group three to five years? and b) Which of these are best suited to be used in the Protecting Teeth @ 3 randomised controlled trial, which investigates the effectiveness and cost-effectiveness of fluoride varnish application in nursery settings?

This review is the first conducted on this specific age group (3-5 years old), which combines both GHQoL and OHQoL measures. There was a previous systematic review that looked at paediatric OHQoL and GHQoL instruments used in oral health research in the whole childhood and adolescence age range (Hettiarachchi et al. 2019). Additionally, there have been several previous reviews of GHQoL measures: a systematic review of GHQoL instruments used

specifically in 0-5-year-old children (Grange et al. 2007), published over a decade ago; a non-systematic overview of GHQoL and some of the disease-specific instruments used in children under five years of age (Germain et al. 2019); and a systematic review of GHQoL measures for children under seven years of age (Verstraete et al. 2020b). In addition, with regards to OHQoL instruments, there was one recent systematic review of the instruments used in children and adolescents with standardized comparison of these instruments (Zaror et al. 2019). The results of the present review were directly compared with the results of previous and recently published GH/OHQoL reviews, and it was found that no other relevant instruments were missed from the present non-systematic review.

The present review identified eleven GHQoL and six OHQoL questionnaires that were used in children aged three to five years (or their parents/guardians as a proxy). The strengths and weaknesses of the identified instruments were assessed in relation to potential use in the PT@3 trial. The main target were parental proxy questionnaires on the child's GHQoL and OHQoL that could be self-administered by the parent/guardian of the child. Inclusion of the full range of HRQoL measures is recommended when conducting economic evaluations of clinical trials, on the grounds that they perform different tasks: a generic non-preference-based measure, a preference-based measure and a disease-specific measure (Drummond 2001, Raat et al. 2006). However, concerns about the measurement burden to the respondent should also be taken into account (Drummond 2001). The shortlisted measures had to be brief, in order not to overburden the respondents, but at the same time they had to have been validated in the UK, or at least in another English-speaking country. Four instruments were selected to be used in the trial, based on the results of the assessment of all identified measures: the CHU9D (a child-centred preference-based HRQoL measure), PedsQL Core (a non-preference-based HRQoL measure, which is often used as a "gold standard"), PedsQL-OH (a short oral health specific add-on to PedsQL Core) and SOHO-5 (an oral health specific measure).

The review has identified only two preference-based GHQoL instruments that were used in children under six years of age: one interviewer-administered (the Quality of Well-Being Scale; QWB), and the other parental self-administered (the

Child Health Utility 9 Dimensions; CHU9D). However, as has been mentioned above, the CHU9D was originally developed with children aged 7-11 years; while QWB is applicable to a wide age range from 4 to 18 years, that is, again, it is not preschooler-specific.

There are no existing preference-based OHQoL measures for preschoolers. A previous systematic review (Zaror et al. 2019) has identified only one oral health-related preference-based measure, the Dental Freetime Trade-Off (DFTO) scale (Fyffe et al. 1999), that was used in teenagers aged 14-19 years. In oral health in general, only limited work has been carried out using utilities or contingent valuation (with participants of various ages from teenagers to older adults), and there have been even fewer applications of these findings in cost-utility or cost-benefit analyses (Vernazza et al. 2012). Vernazza and colleagues identified only one study related to child age, as opposed to adolescents or teenagers, which measured parents' of primary school children willingness to pay (WTP) for two basic dental treatments: sealant (prevention) and filling (cure) (Tianviwat et al. 2008). The results of the present GHQoL and OHQoL measures review indicate the need for further research and development of new preference-based measures suitable for preschoolers or their parents/guardians as a proxy.

There have been some recent advances with regard to new paediatric OHQoL and GHQoL measures being developed. The Caries Impacts and Experiences Questionnaire for Children (CARIES-QC) is a newly developed caries-specific, child-reported measure, which children as young as five years are able to complete with help from parents or a researcher (Gilchrist et al. 2018, Knapp et al. 2018, Knapp 2019). There is ongoing work on turning CARIES-QC into a caries-specific preference-based measure (Rogers et al. 2020). In addition, a new proxy non-preference-based GHQoL measure in very young children (Verstraete et al. 2020b) is under development.

There is a consensus that child self-report should always be used where possible (Marshman et al. 2015), however, proxy reports are considered to be a valuable way of obtaining information about children whose age or cognitive status prevents them from reliably self-reporting (Eiser and Morse 2001, Germain et al.

2019). It is accepted that children under the age of five cannot provide reliable self-reports. Proxy reports are recommended to be used in this case (Wallander et al. 2001, Varni et al. 2007, Matza et al. 2013). At present, no generic preference-based measure that is child-completed with a help of an interviewer is available for the ages 3-5 years. The Chapter 4 review identified only two interviewer administered child non-preference-based GHQoL measures: the TedQL.2 (applicable to the age range 3-8 years) and Kiddy-KINDL (4-6 years). There are also two child-completed interviewer-administered OHQoL instruments (SOHO-5 and CARIES-QC) that were used in children from 5 years of age. However, administering questionnaires to children using one-to-one interviews is highly resource- and time-intensive and could not be implemented in the current study. Moreover, at recruitment the children in the PT@3 Study were three years old, so it is likely they were not developmentally ready to answer the questions, even if a GH/OHQoL instrument was to be interviewer-administered.

7.3.3 Economic evaluation of Protecting Teeth @ 3 trial (Chapters 5 and 6)

Previously, the Childsmile's supervised nursery toothbrushing programme has been shown to be both clinically effective and cost-saving (Macpherson et al. 2013, Anopa et al. 2015), with the largest decrease in modelled costs for the most deprived cohort of children (Anopa et al. 2015). Before this doctoral research project was conducted, the other components of Childsmile had not been formally assessed using economic evaluation methodology. One of the aims of this thesis was to conduct an economic evaluation of a trial based on the nursery fluoride varnish component of Childsmile – the Protecting Teeth @ 3 (PT@3) randomised controlled trial.

The aim of the PT@3 economic evaluation (EE) was to assess the cost-effectiveness of preventive fluoride varnish in the context of the Childsmile programme. The cost-effectiveness of the fluoride varnish (plus treatment as usual) intervention compared with treatment as usual only (control) was estimated using three types of economic analysis: a) a cost–utility analysis (CUA) comparing the costs and QALYs of the two groups over a 24-months period; b) a

cost-effectiveness analysis (CEA) comparing costs and health effects (such as oral health improvement or worsening, as measured by the d3mft index) between the groups; and c) a cost-consequence analysis (CCA) including available costs and outcome measures: the results of the CUA and CEA, as well as other general health and oral health-related quality of life measures employed.

7.3.3.1 Results of the economic evaluation of PT@3 in the context of other research and current policies

The results of the EE indicated that the intervention (fluoride varnish plus treatment as usual; FV plus TAU) was found to be dominated by the comparator (treatment as usual only; TAU only). TAU included all other routine components of the Childsmile programme, apart from fluoride varnish applied in nursery settings. The intervention group had slightly worse outcomes and costed more than TAU only, although all differences in total costs and outcomes between the groups were not statistically significant. This held true in both cases: when the outcome was QALY gained and when the outcome was the change in d3mft (in CEA). This result was also persistent in all CUA sensitivity analysis scenarios.

The cost-effectiveness acceptability curve for the CUA showed that there would be an 11% probability of the FV intervention being cost-effective at a NICE societal willingness to pay threshold of £20,000 per additional QALY (base-case scenario). In all considered sensitivity analysis scenarios this probability was also low (9% to 20%).

The results of the CEA showed that the mean d3mft difference was slightly higher in the intervention group (meaning greater oral health worsening), in comparison with the TAU group, indicating that on average the intervention arm children had a slightly greater worsening of the d3mft. However, the difference in difference between the groups was only 0.071, which was not statistically significant. The results of the probabilistic sensitivity analysis with the d3mft difference in difference as an effectiveness measure showed that in 66% of the 1,000 bootstrap simulations the intervention was more costly and less effective while in 29% the intervention was more costly and more effective.

The results of the CCA indicated that none of the total cost or outcome differences between the two groups (FV plus TAU and TAU only) were statistically significant.

Overall, the results of the EE of the PT@3 trial demonstrate that there were no statistically significant differences in total costs and outcomes between the FV plus TAU and TAU only groups. However, the FV intervention costed on average additional £33 per child in intervention costs over the whole course of the study.

The universal nursery toothbrushing component of Childsmile was previously proven to be both clinically effective (Macpherson et al. 2013) and highly cost-saving, as well as being most cost-saving in the most deprived populations (Anopa et al. 2015). Moreover, a recent Childsmile data linkage study, which aimed to evaluate the reach of the programme and the impact of its components on child oral health (Kidd 2019), indicated that compared to those children who did not participate in the nursery supervised toothbrushing intervention, there was a reduction in the odds of caries experience as the number of years of participation in toothbrushing increased. Children who were participating in nursery toothbrushing for more than three years had substantially reduced odds of caries experience relative to children who were not participating in nursery toothbrushing, with an adjusted odds ratio (aOR) of 0.60 (adjusted for sex, age, SIMD and other Childsmile interventions), 95%CI 0.55, 0.66, with the greatest impact among children in areas of high deprivation. The effect was also apparent with only one year of participation in the toothbrushing programme. On the contrary, nursery FV applications were not independently associated with caries experience. In children targeted for nursery FV, those who actually received FV applications, in comparison to children receiving zero applications, had no reduction in the odds of caries experience regardless of the number applied: in case of five FV applications versus no applications aOR=0.97; 95%CI 0.89, 1.06 (Kidd 2019).

Taking into account the effectiveness of the whole-Scotland universal nursery toothbrushing programme and the cost-saving generated by it, the continuation of the targeted nursery FV component in its current (pre-COVID-19) form and shape in addition to nursery toothbrushing would not be deemed a worthwhile

use of scarce health care resources. Historically, the nursery FV application component of the Childsmile programme was targeted in such a way that each NHS Board would target a minimum of 20% of their nursery and school population, based on their local deprivation scores (NHS Board-level Scottish Index of Multiple Deprivation; SIMD). However, at a later date, a new pressure was added when the delivery of Childsmile fluoride varnish in nurseries, schools and dental practices became a performance target, known as HEAT (Health improvement, Efficiency, Access to treatment, and Treatment) Targets (Scottish Government 2012a, Kidd 2019). With regard to fluoride varnish application, the dental HEAT target stated that "at least 60 per cent of 3 and 4-year-old children in each Scottish Index of Multiple Deprivation (SIMD) quintile to receive at least two applications of fluoride varnish (FV) per year by March 2014". In order to meet this HEAT Target, NHS Boards widened the targeting of the nursery and school fluoride varnish to include more than the most deprived quintile (more than 20%). Childsmile programme monitoring reports illustrate that the majority of the Scottish NHS Boards have been delivering the nursery FV segment of the programme to a greater extent that the initial target of 20%. Moreover, within the 2018/19 academic year, in four NHS Boards around or over 70% of 3-4-year-olds received one or more FV applications (69% to 83% in the individual Boards), which is substantially higher than the combined proportion of children living in the areas from the two most deprived quintiles (SIMD 1 and SIMD 2; 40%) (Childsmile Central Evaluation & Research Team 2019).

Due to the fact that in the PT@3 Study treatment as usual included all other routine components of the Childsmile programme, apart from fluoride varnish applied in nursey settings, it is worth considering what effects the other Childsmile components might have had on the children (in both study groups). The results of the previously referenced Childsmile data linkage study (Kidd 2019) indicated that in addition to children participating in nursery toothbrushing, odds of caries experience were also markedly lower among children regularly attending Childsmile appointments at dental practice (with greater than five visits): OR=0.55; 95%CI 0.50,0.61. However, there were no additional benefits observed for children that received an FV application at every Childsmile dental practice appointment in comparison to those children that never once received an FV application (at their dental practice). It can be

suggested that these results may be explained by the motivation of parents in taking their child to the dentist rather than due to the interventions delivered at the dental practice. However, this hypothesis would have to be explored further with additional research. Previous studies have shown that children and families who attend the dentist regularly may already exhibit behaviours aimed at preventing dental disease irrespective of the family's socioeconomic status (Tickle et al. 1999, Levin et al. 2010), for example, toothbrushing at home. The findings were less clear for dental health support worker contacts (Kidd 2019).

Previous FV clinical effectiveness research, assessed in the 2013 Cochrane systematic review, showed a caries preventive effect in children (Marinho et al. 2013). However, a more recent updated systematic review failed to show such an effect of FV applications (de Sousa et al. 2019), although the methods used in this meta-analysis can be questioned: in order to illustrate the strength of effect the authors used prediction intervals, which have their limitations. Prediction intervals are likely to be imprecise when the meta-analysis is based on a small number of small studies and/or when the studies included in the meta-analysis have a high risk of bias (Riley et al. 2011), whereas the studies included into the review by de Sousa and colleagues were of various population sizes and degrees of risk of bias. Moreover, the inferences based on prediction intervals only hold for contexts that are similar to those on which the meta-analysis is based (IntHout et al. 2016).

Several recent studies also failed to demonstrate the effectiveness of FV. A large randomised trial conducted in Northern Ireland was undertaken in dental practices with children aged two- to three-years-of-age at baseline and followed up for two years (Tickle et al. 2016, O'Neill et al. 2017). A non-significant marginal benefit of FV compared to preventive advice only was found. A Swedish trial aimed to economically evaluate an enhanced caries-preventive programme, which included FV, in comparison with the standard preventive programme in children initially aged 12 months (Anderson et al. 2019). This trial was similar to the PT@3 Study, as their standard programme already comprised of many preventive efforts. The additional intervention was FV and a higher frequency of the other interventions (6-monthly, versus 12-monthly in the control group). At age 36 months, no significant difference in caries prevalence or defs had

occurred between the test and the reference groups. The results of the whole PT@3 study, which included a larger cohort of children than the present EE, indicate that there was a modest non-significant reduction in the worsening of d3mft in the nursery FV group compared to TAU (McMahon et al. 2020). All of the abovementioned studies suggest that the added effectiveness of fluoride varnish is uncertain.

Early childhood caries is more prevalent among the more socially disadvantaged groups (Edelstein 2006, Anil and Anand 2017) and could be related to low socioeconomic status, social exclusion, and sociocultural differences in oral health beliefs and practices (Edelstein 2009). Scottish five-year-olds' epidemiological data shows that although there has been an improvement in child dental health over time within each of the deprivation quintiles, the proportions of children with no obvious decay experience are still considerably lower in the more deprived quintiles (NDIP 2018). There is still a clear social gradient in caries prevalence. It would have been useful to conduct EE analysis by deprivation categories, however, due to low numbers in the EE cohort of the PT@3 Study it was not possible.

Only two previous trials on the cost-effectiveness of fluoride varnish in preschoolers or younger children were identified (O'Neill et al. 2017, Anderson et al. 2019). These studies were briefly described earlier, when discussing the effectiveness of FV. However, these trials varied in their settings, the comparator interventions, and/or participants' ages, hence their results are not directly comparable with the results of the PT@3 EE. The results of the study by O'Neill and colleagues raised concerns about the cost-effectiveness of a fluoride-based intervention (which included 6-monthly FV, provision of free toothbrush and tube of fluoride toothpaste and standardized prevention advice) delivered at dental practices. It showed that the intervention was potentially cost-effective only with respect to reducing carious surfaces (but not for the proportion of children who remained caries-free, nor for the number of episodes of pain) (O'Neill et al. 2017). The Swedish trial (Anderson et al. 2019) found an enhanced caries-preventive programme, which included 6-monthly FV applications, not to be cost-effective. It raised costs without significantly reducing caries development. The results of these studies as well as the results of the PT@3

economic evaluation indicate that the overall cost-effectiveness of FV when compared to other interventions (as opposed to a “do nothing”/no intervention comparator) is questionable.

A review of studies on cost-effectiveness of school-based interventions for caries prevention (Amilani et al. 2020) included two studies on FV, and both found the FV intervention to be cost-effective. However, one of these studies compared FV against fissure sealants in children aged 6-8 years (Neidell et al. 2016), while the other compared FV plus additional interventions against no intervention in adolescents (Bergström et al. 2019). Therefore, these studies’ design and results are not at all comparable to those of the PT@3 Study.

7.3.3.2 General and oral-health-related quality of life measures

No difference between the study groups in the PT@3 Study was found with regard to any of the GH/OHQoL measures at 24 months. Research shows that even in populations of children with dental caries there is a wide variation in impacts that children can experience, with many of them displaying no symptoms at all (Tickle et al. 2002, Rogers et al. 2020). Hence, even oral health specific quality of life instruments may not pick up any substantial signals. The PT@3 population was a combination of caries free children and children with comparatively low d3mft scores from the general population, with around 30% of children having caries at the end of the study (unlike, for example, populations recruited from dental practices, who are already known to require dental treatment), so they were more likely not to exhibit any oral health- and general health-related symptoms.

A previous study found CHU9D, the only available child-centred generic preference-based instrument, to be unresponsive to changes in the dmfs+DMFS index score following caries treatment (Foster Page et al. 2015). It has been suggested that CHU9D might not be sensitive enough to be used as an outcome measure in economic evaluation in the area of paediatric dentistry (Foster Page et al. 2015) and that further psychometric testing of this measure is required, to fully assess its suitability for use in longitudinal studies (Knapp 2019). The results of the PT@3 EE showed that there were no differences in QALYs, utilities or

individual CHU9D item scores between the two study groups. No sub-group analysis was conducted due to low participant numbers in the subgroups. More work exploring the suitability of CHU9D in child oral health research is required, including investigations in most deprived populations and populations with caries.

7.4 Limitations of the study

7.4.1 Systematic review of economic evaluations of primary caries prevention in 2-5-year-old children

One of the limitations of this systematic review is that due to the time constraints only 20% of randomly selected records were assessed or checked independently by a second reviewer. The reporting quality was only formally assessed for full EE studies, because the CHEERS checklist could not be meaningfully used for partial EEs assessment, as many of the items were not applicable. Additionally, the overall methodological quality of the reviewed studies, including any potential sources of bias in the study design or data collection, was not formally assessed.

7.4.2 Instruments for measuring general and oral health-related quality of life in 3-5-year-old children

The main limitation of the present GH/OHQoL instruments review was that it was not a systematic review, but rather it used a snowballing approach, and was narrative in nature. Notwithstanding this fact, the results of this review agreed with those of several recent GHQoL and OHQoL systematic reviews.

With regard to the limitations of the preschoolers' GHQoL and OHQoL instruments themselves, the present review has identified only two preference-based GHQoL instruments that were used in children under six years of age. No preference-based OHQoL measures for children aged 2-5 years (or their proxies) were identified.

7.4.3 Economic evaluation of Protecting Teeth @ 3 trial

There are a number of limitations of the EE of the PT@3 Study. The EE was conducted on a relatively small sample, which did not allow for meaningful subgroup analyses (by deprivation categories or by presence/absence of caries at baseline), as had been planned *a priori*. The time horizon was the duration of the PT@3 trial, namely, 24 months. Hence the EE results do not reflect outcomes throughout later childhood or over the whole life course. It might have been useful to construct, for example, a longer-term Markov model, but this was outside the remit of the current thesis.

7.5 Strengths of the study

7.5.1 Systematic review of economic evaluations of primary caries prevention in 2-5-year-old children

This is the first systematic review of economic evaluations of primary caries prevention with a focus on the preschool age. Search strategies and search terms for this systematic review were carefully thought through and developed based on the standardised EE filters, with the help from a University of Glasgow subject librarian and oral health experts. In addition, several guidance references for undertaking systematic reviews in health care and on conducting systematic reviews of EEs were consulted in the process of developing the protocol for this review. Another strength of this review is that no publication time or language restrictions were applied.

The reporting quality of full EEs was assessed with the Consolidated Health Economic Evaluation Reporting Standards (CHEERS), developed specifically to optimise the reporting of health economic evaluations. Although the reporting quality of partial EEs was not formally assessed, some parameters included in the data extraction template, such as the presence/absence of sensitivity analysis, discount rate, baseline year and perspective used in the analysis, were used to informally assess the reporting quality of partial EEs.

7.5.2 Instruments for measuring general and oral health-related quality of life in 3-5-year-old children

The strength of this review is that it combined both literature searches and expert opinions (from instruments' authors and experts in the fields of GH/OHQoL paediatric research), that were sought for and used in the process of the instrument selection. Moreover, the reviews were searched for using Medline (via the Ovid platform) and Google Scholar, while help was sought from a University of Glasgow subject librarian, a health economist and oral health experts during the development of the search strategies and terms.

7.5.3 Economic evaluation of Protecting Teeth @ 3 trial

One of the strengths of the PT@3 EE was that a bottom-up approach was used in the data collection and calculation of costs and outcomes. This EE has been undertaken as part of a rigorous randomised controlled trial to assess the clinical effectiveness and cost-effectiveness of FV plus TAU and TAU only delivered in nursery/preschool settings. Data were collected prospectively alongside the trial. This approach allowed for a more precise estimation of both costs and outcomes, in comparison with, for example, using assumptions and/or previously published information.

Another strength is that multiple outcomes were measured in the PT@3 Study. These included clinical outcomes (based on d3mft and d3mfs indices) and several quality of life measures: a preference-based GHQoL measure (CHU9D), which allowed calculation of QALYs; a widely used non-preference-based GHQoL measure (PedsQL Core); and two OHQoL measures (PedsQL-OH and SOHO-5). The QALY outcomes allow for the PT@3 intervention to be compared to any other intervention that was evaluated using CUA, both within the oral health area and broader, while the other GH/OHQoL measures allowed assessment of the influence of the intervention and the comparator on various aspects of the child's quality of life. Using an array of different measures ensured that any possible differences between the study groups should be picked up by one or several of the instruments, should they exist.

7.6 Implications of the research for policy making

Childhood is a crucial period for the formation of healthy behaviours as well as providing an opportunity for health-related interventions, which may influence the person throughout their later life (Colak et al. 2013, ICOHIRP 2015). Early interventions have been shown to provide significant long term returns (Heckman 2008, Cunha and Heckman 2010, Scottish Government 2010a, Heckman 2011), especially for preventive programmes aimed at disadvantaged children (Doyle et al. 2007). Therefore, it is of the uttermost importance that child oral health improvement programmes continue in Scotland. Previous research showed that the universal nursery toothbrushing component of the integrated Childsmile programme was associated with child oral health improvements and was cost saving (Macpherson et al. 2013, Anopa et al. 2015). On the other hand, the present doctoral research has indicated that the targeted nursery fluoride varnish segment of Childsmile was not cost effective. With ever tighter budgets at present, it is extremely important to be able to choose wisely between the available interventions. High quality economic evaluations help decision-makers identify and prioritise the most effective and cost-effective interventions and disinvest in the ones that are shown not to be good value for money.

7.6.1 The use of common risk factor upstream approaches

The use of the common risk factor approach, such as promoting breastfeeding and limiting free sugars intake, is recommended by the World Health Organization (WHO 2017b) for controlling early childhood caries together with child obesity. At a population level, upstream approaches are likely to have a greater reach, effectiveness and cost-effectiveness than downstream interventions (Macpherson et al. 2019a), as upstream interventions impact broader social determinants of health (Watt 2007, Peres et al. 2019). Additional upstream changes at the UK or Scotland level can be recommended as part of the advocacy role of the Childsmile programme. Examples include further enforcement of limiting free sugars in foods and drinks and improvement of school nutrition standards. An increase of the current Soft Drinks Industry Levy can be suggested, as well as expanding sugar tax to foods rather than drinks

only, banning of advertising of high-sugar products (to children), and taking high-sugar products off the display and/or child-height shelves in shops. Other avenues that have been shown to be effective in other countries include a vending machine ban, a front-of-package symbol that led to product reformulation, a programme promoting increased water consumption in schools, school fruit and vegetable programmes and healthy marketing campaigns (WCRF 2015, von Philipsborn et al. 2019). There have been some positive changes regarding school nutrition standards in Scotland. For example, a nutrition requirements review for food and drink in Scottish schools published in June 2018 (Scottish Government 2018), which reviewed the existing School Food and Drink Regulations (Scotland) 2008, proposed updates to statutory nutrient standards for primary school lunches. Following extensive consultation and advice from a working group, school food regulations will be amended to ensure, for example, removal of fruit juice and smoothies from primary and secondary schools to help reduce sugar intake, and a minimum of two portions of vegetables and a portion of fruit to be offered as part of a school lunch (Scottish Government 2019b). The initial plan was for the regulations to come into effect by autumn 2020, however, there has been a delay due to the COVID-19 lockdown.

7.6.2 Toothbrushing versus fluoride varnish applications in nursery settings

The results of the effectiveness assessment and economic evaluation of the PT@3 study indicated that there was no statistically significant difference in new caries (worsening of d3mft) between the study groups, and the intervention was found not to be cost-effective, under the trial conditions. In addition, the results of the previous Childsmile evaluation research projects have shown that: a) children targeted for nursery FV, in comparison to children receiving zero applications, had no reduction in the odds of caries experience regardless of the number applied; b) nursery toothbrushing was found to be both clinically effective and cost saving (with the greatest effectiveness and most savings in the most deprived cohorts of children); and c) odds of caries experience were also substantially lower among children regularly attending Childsmile appointments at dental practice.

The combined findings from the previous and present research indicate that toothbrushing interventions in preschool education settings could be recommended over fluoride varnish applications in the same settings, for example, in countries that are looking into the ways of starting their own child caries prevention and/or oral health promotion programmes. Regular child attendance in dental practices should be also encouraged and, ideally, subsidised by governments.

7.6.3 Rethinking child caries prevention policies in the UK

The evidence listed in Section 7.6.2 above would appear to support a suggestion for the delivery of the nursery FV programme to be at least scaled down particularly in those NHS Boards, that cover over 40% of their population (namely, more than the two most deprived quintiles, SIMD 1 and SIMD 2). Any available freed-up resources could be re-distributed to improve and intensify targeting of the nursery and school toothbrushing programme and, potentially, a home toothbrushing intervention, aiming at the most in need and hard to reach families. For example, in Scotland, government-funded early learning and childcare is available for some two-year-olds (such as children from low income families and looked after children) and the funding is being increased from 660 hours to 1140 hours per year (Scottish Government 2019a). These younger children can be also included in the nursery toothbrushing programme and, potentially, a home toothbrushing / oral health intervention. In view of the financial strain that has been caused by COVID-19 and the associated lockdown, those most in need are currently in an even more vulnerable position than they were before.

The first stage of the rethinking process could be to discuss the abovementioned findings, along with other recent research outputs, with relevant stakeholders, in order to come to consensus on the way forward. At the moment, there is some tension between the government policy in relation to FV applications in nurseries and schools and the changing evidence base. A sensitive discussion with the government is required in view of increased funding for FV in recent years in order to reach even more comparatively deprived communities (Scottish Government 2016a) in response to some of the earlier research (Brewster et al.

2013), which showed that there should be more Childsmile resource to NHS Boards with a higher proportion of socially disadvantaged children.

A Delphi-style consultation on best suited strategies for caries prevention in preschool children with the stakeholders across the UK would be one way of progressing this conversation. The consultation would include various types of stakeholders, such as Cochrane representatives, policy makers (e.g. Chief Dental Officers) and researchers. It would focus on finding a consensus on the ways forward – on the development of the relevant guidance and policies.

7.6.4 Restarting Childsmile post COVID-19 lockdown

The COVID-19 pandemic has greatly affected the overall delivery of the Childsmile programme and added new and unprecedented challenges. With most of the programme paused for many months, there are many uncertainties with regards to how and when the components of the programme will remobilise. When re-starting, consideration should be given to emerging evidence and to the best courses of action for prioritising and targeting the most deprived populations.

7.7 Implications and recommendations for future research

7.7.1 The need for high quality economic evaluations in preschooler oral health research

The results of the systematic review in Chapter 3 uncovered the lack of high-quality economic evaluations (EEs) in the area of primary caries prevention in preschoolers. With dental caries being one of the most common diseases affecting humans worldwide the identification of cost-effective prevention strategies in children should be a global public health priority. In order for this to be achieved, studies should be designed to incorporate EEs using best practice methods guidance and adhering to standards for reporting and presenting. Such improvements to the evidence base will serve to increase both the availability and quality of economic evidence in the area of child oral health.

7.7.2 The need for preference-based general health- and oral health-related quality of life instruments for preschoolers

The same systematic review indicated that only one of the included studies used a preference-based GHQoL instrument, which allowed QALY calculation and cost-utility analysis. There is a need to address this gap in the area of preschoolers' oral health research, as using QALY as an outcome measure allows for comparison of various interventions across disease areas and hence can support decision-making on a grander scale (for example, comparisons could be made across the whole of the NHS). One of the reasons for the paucity of cost-utility analyses in young child oral health research could be that there is currently no preference-based instrument available that would suit the needs of EEs in preschooler populations. The only available child-centred preference-based GHQoL instrument, the CHU9D, was not sensitive in child caries research. The results of the GHQoL and OHQoL measures review in Chapter 4 also indicated the need for further research and development of new OH/GHQoL preference-based measures that would be aimed specifically at preschoolers or their parents/guardians as a proxy. At present ongoing research is being conducted in the field of caries specific preference based paediatric measures, such as the work on turning CARIES-QC into a caries-specific preference-based measure (Rogers et al. 2020) and research at Griffith University in Australia and the University of São Paulo, Brazil (Helen Rogers, personal communication, September 2020), but none of them have been published yet.

7.7.3 Proposal for a monetary threshold value of willingness to pay for dmft/dmfs

The Chapter 3 review indicated that many studies used dmft/dmfs as the clinical outcome measure. It could therefore be suggested that a monetary threshold value of willingness to pay for one unit of dmft/dmfs would be established, as was set in Sweden for adult teeth (a cost per saved DEFS of < EUR 120 is considered low; of EUR 120 – 240, moderate; of EUR 240 – 600, high; and of > EUR 600, very high) (Anderson et al. 2019). This would allow for benchmarking and a meaningful comparison of the cost-effectiveness results in child caries research.

7.7.4 Investigation of psychometric properties of CHU9D, PedsQL Core, PedsQL-OH and SOHO-5 in the context of oral health research

Another possible future research area is a psychometric properties investigation based on the data collected in the PT@3 Study – for all of the instruments used in the trial (CHU9D, PedsQL Core, PedsQL-OH and SOHO-5), in order to assess their suitability for being used in preschoolers (via their parents/guardians as a proxy) within the general population.

7.7.5 Further economic evaluation research in most deprived children / Investigating inequalities

Previous research indicates that children from deprived backgrounds have higher caries rates leaving them at a disadvantage compared with their wealthier and healthier peers (Watt et al. 2018). Within the EE of the PT@3 Study, it was not possible to conduct subgroup analysis based on deprivation groups due to low numbers in each subgroup. Further studies that would investigate the additional effectiveness and cost-effectiveness of FV in the most deprived children can be recommended, as well as looking deeper into how to address persisting oral health inequalities.

7.7.6 Economic evaluation of other segments of Childsmile

To date only the nursery toothbrushing and nursery based FV segments of the integrated Childsmible programme have been assessed economically. It is recommended that EEs should be conducted on the remainder of the Childsmile components. These would provide a fuller picture with regards to the cost-effectiveness of Childsmile overall.

7.8 Conclusions

The results of the systematic review of economic evaluations of primary caries prevention in two- to five-year-old preschool children (Chapter 3) found a paucity of high-quality economic evaluations in the area. The results indicated that although the number of economic evaluations studies relating to caries prevention interventions in preschoolers has been increasing in recent years,

several items of the Consolidated Health Economic Evaluation Reporting Standards (CHEERS) checklist were inadequately reported in a substantial proportion of the reviewed studies. The review has highlighted wide variation in: a) types of caries prevention interventions investigated; b) effectiveness measures used; c) how costs and outcomes are reported; and d) study perspective (when indicated).

Importantly, only one study employed cost-utility analysis, using a preference-based outcome measure. This notable lack of use of preference-based health-related quality of life measures in the field of preschoolers' oral health likely reflects the challenges with conducting economic evaluations in this young age group, the availability of suitable preference-based measures, and also flags up the limitations with the use of these studies for the purposes of decision making in dental healthcare.

While variation in prevention interventions investigated is entirely expected, the methodological limitations identified preclude meaningful comparisons across studies as well as compromise the evidence base for strategies in relation to the prevention of this disease in this age group. Due to the small numbers of studies investigating each intervention type (for example, fluoride varnish, oral health education, dental sealants, toothbrushing, fluoridated food and drinks, water fluoridation) and questionable methodological quality of many of the reviewed economic evaluations, it was not possible to arrive at reliable conclusions with regards to the economic value of primary caries prevention.

With dental caries being one of the most common diseases affecting humans worldwide, the identification of cost-effective prevention strategies in children should be a global public health priority. This agrees with the recommendations in recent articles outlining the challenges and priorities for global oral health. In order for this to be achieved, studies should be designed to include economic evaluations using best practice methods guidance and adhering to standards for reporting and presenting. Such improvements to the evidence base will serve to increase both the availability and quality of economic evidence in this important area.

The review of general health and oral health-related quality of life measures used in three- to five-year-old children (Chapter 4) identified a range of existing questionnaires for use in preschool populations – both for parental proxy reporting and child self-reporting. Their strengths and limitations were considered in relation to applying them in the PT@3 Study (a preschoolers' oral health randomised controlled trial). Four instruments were selected to be used in the trial: the CHU9D, PedsQL Core, PedsQL-OH and SOHO-5. The results of Chapter 4's review can assist researchers and programme evaluators in understanding the differences between the included general health and oral health-related quality of life measures and to help them in choosing the best-suited instrument(s) for their projects.

With regard to the limitations of the preschoolers' general health and oral health-related quality of life instruments themselves, this review has identified only two preference-based general health-related quality of life instruments that had been used in children under six years of age: one interviewer-administered (QWB), and the other parental self-administered (CHU9D). Even then, the CHU9D was originally developed with children aged 7-11 years, rather than with preschool children; while QWB is applicable to a wide age range from 4 to 18 years (it is not preschooler specific). No preference-based oral health-related quality of life measures for preschoolers were identified. Further research and development of new preference-based measures suitable for preschoolers (or their parents/guardians as a proxy) are required.

The findings of the economic evaluation of the PT@3 Study (Chapter 6) demonstrate that there was no statistically significant difference in total costs, QALYs accumulated, and in several general health and oral health-related quality of life measures at 24 months (CHU9D utility, PedsQL, PedsQL-OH and SOHO-5 scores) between the two study groups. There was no statistically significant difference in new caries development between the two groups. The results show that applying fluoride varnish (FV) in nursery settings in addition to the existing treatment a usual (which was all other components of the Childsmile programme, apart from nursery FV) is not cost-effective. In view of previously proven clinical effectiveness and economic worthiness of the universal nursery toothbrushing component of Childsmile, which was shown to be highly cost

saving, as well as being most effective and cost saving in most deprived populations, it seems that the continuation of the targeted nursery FV programme in its most recent (pre-COVID-19) form and shape in addition to nursery toothbrushing and other routine Childsmile components needs to be reviewed in consultation with policy makers. The findings of the economic evaluation of the PT@3 Study will be used to inform the future Childsmile strategic policy development. The results should form part of the evidence to inform the Scottish, UK, and international guidance on community-based child oral health promotion programmes.

Appendices

Appendix 1 Cost-utility analysis: direct elicitation of preferences

There are two main ways of estimating the economic values attached to non-market goods and services: revealed preferences (indirect approach) and stated preferences (direct approach). An example of a revealed preference approach in healthcare would be the measurement of the travel costs incurred to attend a dentist. Stated preference approaches are based on hypothetical or constructed markets. They ask people to state what economic value they attach to those goods and services (Edwards and McIntosh 2019).

Stated-preference methods fall into two broad categories: a) Methods using direct elicitation of monetary values of an intervention (including contingent valuation or willingness-to-pay and willingness-to-accept methods); and b) Methods using ranking, rating, or choice designs to quantify preferences for various attributes of an intervention (often referred to as conjoint analysis, discrete-choice experiments, or stated-choice methods) (Bridges et al. 2011). A simple distinction between these two categories is that the former aims to estimate demand for a single product, whereas the latter aims to explore trade-offs between a product's attributes and its effect on choice. However, in practice, the distinctions between the two categories have blurred, with researchers estimating demand using multiple-question and discrete-choice formats, or, on the other hand, using preference estimates to calculate willingness-to-pay for attributes (Bridges et al. 2011). The most widely used methods of direct preference elicitation, such as visual analogue scale, time trade-off and standard gamble are described below.

The visual analogue scale (VAS) is a form of rating scale. It is the simplest of the direct methods and involves the use of a scale shown on a single line. The top of the scale indicates the “best imaginable health”, whereas the bottom of the scale indicates the “worst imaginable health”. Individuals are asked to indicate where on the scale they consider the health state of interest to be. VAS is generally considered to be inferior to the standard gamble and time trade-off, due to involving a rating task rather than a choice task, and also due to scaling biases. Scaling biases include the end-of-scale bias, where participants are reluctant to place health states at the extreme ends of the scale. However, the simplicity of the VAS means that it is a useful tool often used as an exercise before other methods (Whitehead and Ali 2010).

The time trade-off (TTO) is a choice-based method that establishes for an individual how much time in full health is equivalent to a specified period of time spent in a particular ill-health state (Thorrington and Eames 2015). The TTO method presents individuals with two alternative scenarios and asks which they would prefer. The choice is between living for the rest of their life in an impaired health state (for instance, type 2 diabetes), or living in full health for a shorter period of time. The time period spent in full health is varied until the individual is indifferent between the two choices. Hence, participants are asked how much time they would be willing to sacrifice to avoid an impaired health state (Whitehead and Ali 2010). Many researchers prefer employing the TTO

elicitation format, because subjects may find the standard gamble (SG) elicitation format (described below) difficult. However, longevity trade-offs may be unacceptable for acute conditions where reduced life expectancy is not a clinically relevant outcome (Johnson et al. 2009).

The standard gamble (SG) is another choice-based method that identifies the probability of being in a better health state that makes an individual indifferent between the certainty of being in an intermediate health and a gamble between a worse health state and a better health state (Thorrington and Eames 2015). The SG involves an element of risk in the decisions faced by individuals. The choice is between the certainty of remaining in a particular health state or taking a gamble of either being in full health or risking death. The probability of experiencing death is varied until the individual is indifferent between the certainty and the gamble. The more severe the health state, the greater is the risk of death that the patient would accept to be cured of it (Whitehead and Ali 2010).

References:

Bridges, J. F. P., A. B. Hauber, D. Marshall, A. Lloyd, L. A. Prosser, D. A. Regier, F. R. Johnson and J. Mauskopf (2011). "Conjoint Analysis Applications in Health—a Checklist: A Report of the ISPOR Good Research Practices for Conjoint Analysis Task Force." Value in Health 14(4): 403-413.

Edwards, R. T. and E. McIntosh (2019). Applied health economics for public health practice and research, Oxford University Press.

Johnson, F. R., A. B. Hauber and S. Özdemir (2009). "Using Conjoint Analysis to Estimate Healthy-Year Equivalents for Acute Conditions: An Application to Vasomotor Symptoms." Value in Health 12(1): 146-152.

Thorrington, D. and K. Eames (2015). "Measuring Health Utilities in Children and Adolescents: A Systematic Review of the Literature." PloS one 10(8): e0135672-e0135672.

Whitehead, S. J. and S. Ali (2010). "Health outcomes in economic evaluation: the QALY and utilities." British Medical Bulletin 96(1): 5-21.

Appendix 2 Cost-benefit analysis: valuing benefits in monetary terms

The theoretical base for the measurement of benefits in CBA is economic welfare theory and the concept of consumer surplus. Consumer's surplus is defined as the difference between willingness to pay (WTP) for a good and what is actually paid (Johannesson and Jönsson 1991). WTP is the theoretically correct benefit measure in welfare theory and cost-benefit analysis. WTP is the maximum amount of money an individual is prepared to give up to secure that a proposed project/health improvement is undertaken. If compensating variation is used, the individual is held on the initial level of utility (satisfaction) and then willingness to pay for improvement in health is investigated (Johannesson and Jönsson 1991).

In the case of a good or service traded in a competitive market, buyers and sellers reveal their preferences directly through their actions, where price and quantity signals are absorbed, hence allowing compensating variation to be estimated directly. This method of eliciting welfare changes is called revealed preference (McIntosh et al. 2010, Edwards and McIntosh 2019). Compensating variation is the amount of money we can take away from an individual after an economic exchange, while living her/him as well off as she/he was before it. For a welfare gain, it is the amount she would be willing to pay for a change. For welfare loss, it will be the amount she would need to accept as compensation for the change. Compensating variation is the preferred measure in CBA. However, in healthcare, market failure exists and thus extensive government intervention is required and healthcare, preventive healthcare, and PHIs are often provided publicly. In this case people are not revealing their preferences by how much they pay for healthcare goods and services. Is a result of market failure, individuals preferences are not revealed in the usual manner by how much people pay for good or service. There are a number of methods to measure the individual's willingness to pay (WTP) for nor non-marketed goods. For example, stated preference survey techniques, the Clarke-Groves mechanism, travel cost methods, and hedonic approaches (McIntosh et al. 2010, Edwards and McIntosh 2019).

In CBA, valuation methods can be categorised as direct and indirect. Indirect methods such as the travel cost approach, use actual choices made by consumers to develop models of choice (McIntosh et al. 2010). Direct methods ask consumers what they would be willing to pay or accept (WTP/WTA) for a change in a good or service. Direct methods are examples of compensating variation stated preference techniques, when individuals do not actually make any behavioural changes, but rather only state that they would behave in this fashion. In health economics the direct methods are often the best option. In case of healthcare, consumers (members of the population or potential patients) may have little or no experience of the healthcare service or good requiring valuation, and actual choices for treatments / preventive services are often heavily influenced by advice from medical professionals (this is asymmetry of information) (Edwards and McIntosh 2019).

Both direct and indirect methods have advantages and disadvantages. Direct methods are criticized because of the hypothetical nature of the questions and the fact that actual behaviour is

not observed. However, direct methods provide the main viable alternative to valuing goods and services where the consumer may have had little or no experience of the good being valued, which is often the case in health and environmental economics (McIntosh et al. 2010).

In health economics, contingent valuation (CV) is a method that elicits an individual's monetary valuations of health programmes or health states (Bayoumi 2004). CV method is a stated preference approach designed to estimate monetary welfare gains or losses directly. CV survey is typically aimed to obtain an accurate estimate of the benefits of a change in the level of provision of good, which can then be combined with the costs of producing the good, within a CBA (Edwards and McIntosh 2019). Contingent valuation methods use surveys to elicit people's preferences for goods by finding out what they would be willing to pay (or accept) for specified improvements (or downgradings) in them (McIntosh et al. 2010). The questions can be framed to ask individuals how much they would pay to obtain positive changes in health status or avoid negative changes in health status, this is called "willingness to pay" (WTP), or how much they would need to be paid to compensate for a decrease in health status or for foregoing an improvement in health status ("willingness to accept"; WTA). In general, WTP questions yield more accurate and precise valuations than WTA questions. WTP values are typically used as outcomes within CBA studies (Bayoumi 2004).

The first stage of designing a CV study is the scenario description (McIntosh et al. 2010). The scenario description contains information on all relevant aspects of the product/service being valued and is what the respondents will read/listen to prior to the CV task. The scenario description has to be realistic to the respondent and conveyed in a form that is both informative and understandable. The description contains the information on the payment vehicle - the type of payment being asked of the respondent, for example, additional income tax, charitable donation, or monthly payments. The payment vehicle has to be chosen in a way that respondents can easily understand and fit into the scenario being described.

There are several instrumentation techniques that can be used in CV studies: direct face-to-face interviews, telephone interviews and mail/online surveys. The choice of the instrumentation technique is a trade-off between the ability to describe things in detail and be sure that the respondent has understood the task versus the ease and ability to achieve large sample sizes. As a general rule, face-to-face interviews are regarded as the best form of instrumentation, but this is subject to resource constraints (McIntosh et al. 2010).

CV studies may use different elicitation formats (McIntosh et al. 2010). The elicitation format refers to the style of questioning to elicit the WTP/WTA value. There are a number of different formats to choose from (each with its own strengths and weaknesses), and there is little consensus in the health care literature concerning which is superior. The following elicitation formats are briefly described below: open-ended question, iterative bidding, payment scale, Closed-ended questions, closed ended with follow-up, and marginal approach.

The open-ended question is the 'simplest' of the elicitation designs. This question asks for the WTP for a health care intervention without any prompts or cues from the questionnaire or interviewer. In iterative bidding, the question is designed so that it resembles an auction as the respondent enters a bargaining process with the interviewer. The process can be likened to a "haggle" technique happening in real-life markets making it more familiar to the respondents. The respondent is presented with a first-bid and depending on whether they accept or reject that bid; it is either raised or lowered till eventually the respondent's maximum WTP is reached. The payment scale question presents respondents with a range of values to choose from. A typical design presents respondents with a series of bid amounts, in a vertical list from the lowest bid (top) to the highest bids (bottom) in increments. Typically, respondents are requested to put a tick mark next to the amounts that they are sure they would pay, put a cross mark next to the amounts they are sure they would not pay, and circle their maximum WTP. Closed-ended questions are designed to lead to a yes/no response. Respondents are presented with a bid and are asked if they are WTP that amount. An example of such a question is: "Do you think that having the health care intervention is worth £100?", and in response a "Yes" / "No" box should be ticked. The closed ended with follow-up technique is an extension of the closed-ended method: to obtain more information from each respondent a follow-up open-ended question is inserted. The marginal approach asks individuals to firstly consider what treatment or service they prefer and then to reveal their maximum WTP value to have their preferred option over their less preferred option. Instead of the absolute WTP being elicited, it is the relative WTP that is being revealed. An example question is: "What is the maximum amount of money you would be prepared to pay to receive your most preferred option instead of your least preferred option?"

Another method of direct preference elicitation used in CBA is conjoint analysis. Apart from health economics, conjoint analysis methods have been widely used and validated in marketing research, transportation, and environmental economics (Johnson et al. 2009). Conjoint analysis is the analytical technique used in discrete choice experiments (DCE), which is used in healthcare to evaluate preferences from participants for different attributes of an intervention, without directly asking them to state their preferred options (York Health Economics Consortium 2016a). Conjoint analysis surveys involve comparing hypothetical scenarios by ranking, rating, or choosing a particular scenario. These choices indicate the relative importance of the product attributes and provide data for estimating utility functions (Phillips et al. 2002). Conjoint analysis is increasingly used in health economics to calculate patients' and physicians' stated preferences for health-care interventions, treatment alternatives, and health-care services (Johnson et al. 2009).

In a DCE participants are typically presented with a series of alternative hypothetical scenarios containing a number of variables or "attributes" (usually less or equal to five), each of which may have a number of variations or "levels". Participants are asked to state their preferred choice between two or three competing scenarios, each of which consists of a combination of these attributes/levels. Survey instruments usually include 5-10 of such choices to be completed. Preferences are revealed without participants explicitly being asked to state their preferred level for each individual attribute. For example, a pharmaceutical company might be interested in

determining patient preferences for a painkiller provided either as a tablet or liquid formulation. Attributes (and levels) tested in a DCE might consist of “time for painkiller to work” (<10 minutes, 10-30 minutes, >30 minutes), “convenience” (inconvenient, convenient) and “number of repeat doses required” (0, 1-2, ≥3) (York Health Economics Consortium 2016b).

References:

Bayoumi, A. M. (2004). "The measurement of contingent valuation for health economics." Pharmacoeconomics 22(11): 691-700.

Bridges, J. F. P., A. B. Hauber, D. Marshall, A. Lloyd, L. A. Prosser, D. A. Regier, F. R. Johnson and J. Mauskopf (2011). "Conjoint Analysis Applications in Health—a Checklist: A Report of the ISPOR Good Research Practices for Conjoint Analysis Task Force." Value in Health 14(4): 403-413.

Edwards, R. T. and E. McIntosh (2019). Applied health economics for public health practice and research, Oxford University Press.

Johannesson, M. and B. Jönsson (1991). "Economic evaluation in health care: Is there a role for cost-benefit analysis?" Health Policy 17(1): 1-23.

Johnson, F. R., A. B. Hauber and S. Özdemir (2009). "Using Conjoint Analysis to Estimate Healthy-Year Equivalents for Acute Conditions: An Application to Vasomotor Symptoms." Value in Health 12(1): 146-152.

McIntosh, E., P. Clarke, E. Frew and J. Louviere (2010). Applied methods of cost-benefit analysis in health care, Oxford University Press.

Phillips, K. A., T. Maddala and F. R. Johnson (2002). "Measuring preferences for health care interventions using conjoint analysis: an application to HIV testing." Health services research 37(6): 1681-1705.

Thorrington, D. and K. Eames (2015). "Measuring Health Utilities in Children and Adolescents: A Systematic Review of the Literature." PloS one 10(8): e0135672-e0135672.

Whitehead, S. J. and S. Ali (2010). "Health outcomes in economic evaluation: the QALY and utilities." British Medical Bulletin 96(1): 5-21.

York Health Economics Consortium. (2016a). "Glossary. Health Economic Terms. Conjoint Analysis." Retrieved August, 2020, from https://yhec.co.uk/glossary/conjoint-analysis/.

York Health Economics Consortium. (2016b). "Glossary. Health Economic Terms. Discrete Choice Experiment (DCE)." Retrieved August, 2020, from https://yhec.co.uk/glossary/discrete-choice-experiment-dce/.

Appendix 3 General search strategy adapted to each database (Medline example)

1. Economics/
2. exp "Costs and Cost Analysis"/
3. Economics, Nursing/
4. Economics, Medical/
5. Economics, Pharmaceutical/
6. exp Economics, Hospital/
7. Economics, Dental/
8. exp "Fees and Charges"/
9. exp Budgets/
10. budget*.ti,ab,kf.
11. (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ti,kf.
12. (economic* or cost or costs or costly or costing or price or prices or pricing or pharmacoeconomic* or pharmaco-economic* or expenditure or expenditures or expense or expenses or financial or finance or finances or financed).ab./freq=2
13. (cost* adj2 (effective* or utilit* or benefit* or minimi* or analy* or outcome or outcomes)).ab,kf.
14. (value adj2 (money or monetary)).ti,ab,kf.
15. exp models, economic/
16. economic model*.ab,kf.
17. markov chains/
18. markov.ti,ab,kf.
19. monte carlo method/
20. monte carlo.ti,ab,kf.
21. exp Decision Theory/
22. (decision* adj2 (tree* or analy* or model*)).ti,ab,kf.
23. or/1-22
24. ("Cost analys*" or "Cost of illness" or "cost adj saving*" or "burden of illness" or "financial impact*" or "resource impact*" or "opportunity cost*" or (("multicriteria" or "multi criteria" or "multi-criteria") and "decision analysis") or MCDA or "value for money" or "return on investment").ti,ab,kf.
25. 23 or 24
26. ("oral health" or caries or carious or (("early childhood" or ECC) and caries) or dent* or (dent* and decay)).ti,ab.
27. (toothbrush* or "tooth-brush*" or (tooth adj1 brush*) or toothpaste or (tooth adj1 paste) or fluorid* or (chlorhexidine and (oral or dent*)) or "fissure sealant*" or "dental sealant*" or mouthwash* or "mouth wash*" or "mouth-wash*" or (mouth adj1 wash*) or (flossing and dent*) or "dental floss*" or ((preventive adj2 programme*) and ("oral health" or dent*)) or ((educat* or prevent* or promotion) and ("oral health" or dent*))).ti,ab.

28. 26 or 27
29. exp Child, Preschool/
30. (toddler* or infant? or "pre school*" or "preschool*" or "preschool*" or "early childhood" or "young child*" or nurser* or kindergarten* or "early years" or (("day care" or daycare or "day-care") adj child*)).ti,ab.
31. 29 or 30
32. 25 and 28 and 31
33. exp Review Literature as Topic/
34. Review.pt.
35. Review/
36. 33 or 34 or 35
37. 32 not 36

Appendix 4 The CHEERS checklist

Section/item	Item No	Recommendation	Rating: Reported / Not reported / Not applicable 1 (yes) / 0 (no) / N/A
Title and abstract			
Title	1	Identify the study as an economic evaluation or use more specific terms such as "cost-effectiveness analysis", and describe the interventions compared.	
Abstract	2	Provide a structured summary of objectives, perspective, setting, methods (including study design and inputs), results (including base case and uncertainty analyses), and conclusions.	
Introduction			
Background and objectives	3	Provide an explicit statement of the broader context for the study.	
		Present the study question and its relevance for health policy or practice decisions.	
Methods			
Target population and subgroups	4	Describe characteristics of the base case population and subgroups analysed, including why they were chosen.	
Setting and location	5	State relevant aspects of the system(s) in which the decision(s) need(s) to be made.	
Study perspective	6	Describe the perspective of the study and relate this to the costs being evaluated.	
Comparators	7	Describe the interventions or strategies being compared and state why they were chosen.	
Time horizon	8	State the time horizon(s) over which costs and consequences are being evaluated and say why appropriate.	
Discount rate	9	Report the choice of discount rate(s) used for costs and outcomes and say why appropriate.	
Choice of health outcomes	10	Describe what outcomes were used as the measure(s) of benefit in the evaluation and their relevance for the type of analysis performed.	
Measurement of effectiveness	11a	*Single study-based estimates:* Describe fully the design features of the single effectiveness study and why the single study was a sufficient source of clinical effectiveness data.	
	11b	*Synthesis-based estimates*: Describe fully the methods used for identification of included studies and synthesis of clinical effectiveness data.	
Measurement and valuation of preference based outcomes	12	If applicable, describe the population and methods used to elicit preferences for outcomes.	
Estimating resources and costs	13a	*Single study-based economic evaluation:* Describe approaches used to estimate resource use associated with the alternative interventions. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe	

Section/item	Item No	Recommendation	Rating: Reported / Not reported / Not applicable 1 (yes) / 0 (no) / N/A
		any adjustments made to approximate to opportunity costs.	
	13b	*Model-based economic evaluation:* Describe approaches and data sources used to estimate resource use associated with model health states. Describe primary or secondary research methods for valuing each resource item in terms of its unit cost. Describe any adjustments made to approximate to opportunity costs.	
Currency, price date, and conversion	14	Report the dates of the estimated resource quantities and unit costs. Describe methods for adjusting estimated unit costs to the year of reported costs if necessary. Describe methods for converting costs into a common currency base and the exchange rate.	
Choice of model	15	Describe and give reasons for the specific type of decision-analytical model used. Providing a figure to show model structure is strongly recommended.	
Assumptions	16	Describe all structural or other assumptions underpinning the decision-analytical model.	
Analytical methods	17	Describe all analytical methods supporting the evaluation. This could include methods for dealing with skewed, missing, or censored data; extrapolation methods; methods for pooling data; approaches to validate or make adjustments (such as half cycle corrections) to a model; and methods for handling population heterogeneity and uncertainty.	
Results			
Study parameters	18	Report the values, ranges, references, and, if used, probability distributions for all parameters. Report reasons or sources for distributions used to represent uncertainty where appropriate. Providing a table to show the input values is strongly recommended.	
Incremental costs and outcomes	19	For each intervention, report mean values for the main categories of estimated costs and outcomes of interest, as well as mean differences between the comparator groups. If applicable, report incremental cost-effectiveness ratios.	
Characterising uncertainty	20a	*Single study-based economic evaluation:* Describe the effects of sampling uncertainty for the estimated incremental cost and incremental effectiveness parameters, together with the impact of methodological assumptions (such as discount rate, study perspective).	
	20b	*Model-based economic evaluation:* Describe the effects on the results of uncertainty for all input parameters, and uncertainty related to the structure of the model and assumptions.	
Characterising heterogeneity	21	If applicable, report differences in costs, outcomes, or cost-effectiveness that can be explained by variations between subgroups of patients with different baseline characteristics or other observed variability in effects	

Section/item	Item No	Recommendation	Rating: Reported / Not reported / Not applicable 1 (yes) / 0 (no) / N/A
		that are not reducible by more information.	
Discussion			
Study findings, limitations, generalisability, and current knowledge	22	Summarise key study findings and describe how they support the conclusions reached. Discuss limitations and the generalisability of the findings and how the findings fit with current knowledge.	
Other			
Source of funding	23	Describe how the study was funded and the role of the funder in the identification, design, conduct, and reporting of the analysis. Describe other non-monetary sources of support.	
Conflicts of interest	24	Describe any potential for conflict of interest of study contributors in accordance with journal policy. In the absence of a journal policy, we recommend authors comply with International Committee of Medical Journal Editors recommendations.	

Appendix 5 Partial EEs: Study aim, participants and settings description, interventions and comparators

First author (year of publication), country	Aim of study	Type of economic evaluation	Participants' age / Number of participants (within 2-5 y.o. range)	Participant description	Setting	Intervention(s)	Comparator(s)
Anopa (2015), UK	To compare the cost of providing the Scotland-wide nursery toothbrushing programme with associated National Health Service cost savings from improvements in the dental health of five-year-old children: through avoided dental extractions, fillings and potential treatments for decay.	Cost analysis	3 and 4 y.o. Numbers varied in different study years. E.g. in 2009/10 it was 111,688 (3-4 y.o.)	The total population of 3-4 y.o. in Scotland	Nurseries (kindergartens)	Supervised toothbrushing in nurseries and toothpaste packs for home use.	No supervised nursery toothbrushing
Ast (1970), USA	To compare costs of dental care for children who drank fluoridated water from infancy with the costs for those children who did not.	Cost analysis	5 and 6 y.o. Fluoridated area: 5y.o. = 205, 6y.o.= 182; Non-fluoridated area: 5y.o. = 197, 6y.o.= 182.	Children residing in poorest socioeconomic areas of a fluoridated city and a non-fluoridated city.	School based dental programme. (Mobile dental trailer staffed by a dentist and dental assistant.)	Artificial water fluoridation. Fluoridated vs non-fluoridated area. (Enrolled into the study at 5-6 y.o, lifetime residents in the F area.)	Children living in a non-fluoridated area.
Buckingham (2017), UK	To report on the feasibility and costs of a pilot oral health improvement programme with FV applications in school/preschool settings, and on any impact on dental decay levels.	Cost analysis	2 study sites with chn aged 3-4 years (n=150); 1 site with chn aged 4-5 years (n=50); 1 site with chn aged 4-7 years (n=189)	Children attending preschools and primary schools within areas of deprivation and where dental data and local knowledge indicated relatively high levels of dental decay.	Preschools and schools	Daily supervised toothbrushing in the schools; oral health education was provided for children, parents and school staff to encourage toothbrushing at home, improve diet and visit a dentist regularly; parents	No comparator

First author (year of publication), country	Aim of study	Type of economic evaluation	Participants' age / Number of participants (within 2-5 y.o. range)	Participant description	Setting	Intervention(s)	Comparator(s)
						of children who needed treatment were sent letters signposting them to local dental practices; three applications of FV per year were offered.	
Chen (2009), Taiwan	To examine dental service utilization and costs before and after the introduction of fluoride gel application for preschool children in Taiwan.	Cost analysis	Children aged ≤5 years old. 101,314 in total: 50,657 in the study group (fluoride gel) and 50,657 in the control group (no fluoride gel applied), matched by gender, age and geographical region. Of these, 48,778 children in the study group and 48,778 in the control group were aged 2-5 years.	Study group: all preschool children aged ≤5 years old who received fluoride gel application from dental clinics or hospital dentistry departments between 1 July and 31 December, 2004.	Dental clinics and hospital dentistry departments	Fluoride gel application and providing information about oral hygiene to parents (in dental clinics)	Children aged ≤5 years who visited dental clinics or hospital dentistry departments without receiving fluoride gel applications (matched with the study group children by gender, age and geographical region).
Dowell (1976), UK	To assess the maximum economic level of expenditure on fluoridation of the water supply, using the	Cost analysis	The overall estimation is for a standardised population of 100,000 of all ages. Some	See "Number of participants".	General population.	Artificial water fluoridation	None.

First author (year of publication), country	Aim of study	Type of economic evaluation	Participants' age / Number of participants (within 2-5 y.o. range)	Participant description	Setting	Intervention(s)	Comparator(s)
	available data.		calculations included preschool children (aged 3-4 years). The total number of 3-4 y.o. used in the calculations is not always clearly stated (as different sources were used), but there were 3,095 children aged 3-4 y in the standardised population.				
Edelstein (2015), USA	To model disease reductions and cost savings from ECC management alternatives	Cost analysis	0-5 years (inclusive). 450,000 children younger than 6 years eligible for New York State Medicaid (56% in New York City).	See above	Various settings. Many interventions vere compared using modelling.	9 preventive interventions are compared (with several simulations/scenarios per each intervention): water fluoridation, fluoride varnish, fluoride toothpaste toothbrushing, medical screening and fluoride varnish application, bacterial transmission reduction, motivational interviewing, dental prevention visits, secondary prevention, and combinations	Many interventions vere compared using modelling. See above.

First author (year of publication), country	Aim of study	Type of economic evaluation	Participants' age / Number of participants (within 2-5 y.o. range)	Participant description	Setting	Intervention(s)	Comparator(s)
Fidler (1977), UK	To empirically determine the differences in treatment patterns and reductions in treatment costs as a result of fluoridation.	Cost analysis	Children and young adults up to the age of 21 y. 2-4 y.o. group: n=207 in fluoridated area (Watford, UK); n=132 in adjacent non-fluoridated areas.	Children living in either the fluoridated area or in adjacent non-fluoridated areas. The treatment and cost comparisons were made based on the data on individuals seeking treatment between Dec 1973 and March 1974.	Children and young adults residing in either fluoridated area (Watford, UK) or an adjacent non-fluoridated area.	Artificially fluoridated area: children and young adults continuously residing in Watford, UK. The group of interest, 2-4 y.o., were exposed to fluoride for the whole duration of their lives.	Non-fluoridated areas adjacent to Watford, UK.
Gisselsson (1994), Sweden	To evaluate the effect of chlorhexidine gel treatment on the incidence of approximal caries in preschool children.	Cost analysis	4 y.o. 117 in study groups: 59 in chlorhexidine gel group, and 58 in placebo gel group. 116 in control group.	Total population of children born in 1983 in a small industrial town in Sweden was invited into the study. Out of these, 117 completed the study. The control group consisted of children living in the same town born in Aug-Dec, 1982 and in Jan-June, 1984; 116 of these participated in the final dental examination.	Clinic (Public Dental Service Clinic)	Professional flossing and chlorhexidine gel (4 times a year for 3 years), underlined with home toothbrushing (250ppm F) and taking fluoride tablets at home (some participants were taking them regularly, but other were not).	Control group with no interventions.
Hawkins (2004), Canada	To compare the costs and patient acceptability of two methods of professionally applied topical fluorides (PATF):	Cost analysis	Mean age 8.0 years; 256 children aged 3-15 years; 30% (77	Schoolchildren **[and kindergarten(?), as lower age was 3 y.o.]** who were identified as requiring PATF by a schol-	Public health dental clinic for preventive care	Topical fluoride applications were provided within public health settings. Following the dental screening, the parent of	Fluoride varnish vs fluoride foam

First author (year of publication), country	Aim of study	Type of economic evaluation	Participants' age / Number of participants (within 2-5 y.o. range)	Participant description	Setting	Intervention(s)	Comparator(s)
	foam and varnish.		children) were aged 6 years and younger	based dental screening programme delivered by Ontario health units. They were considered to be at high risk of dental caries because they had at least one smooth surface carious lesion.		each child was informed of the study and consent was obtained for the delivery of PATF and inclusion in the study. Children received from dental hygienists either fluoride foam applied with Styrofoam trays or fluoride varnish painted on tooth surfaces. Subjects were assigned to groups based on the time of day they were scheduled to have fluoride treatment. Fluoride foam was applied for morning appointments and varnish was applied during afternoon appointments.	
Hirsch (2012), USA	To determine which interventions, singly and in combination, could have the greatest effect in reducing caries experience and cost in a population of children aged birth to 5 years.	Cost analysis	431,070 children in Colorado's population of 0-5-y.o.: 8.2% were aged 0-6mo, 24.7% were 7-24 mo, and 67.1% were 25-72 mo.	See above.	Various settings. Many interventions were compared using modelling.	6 categories of ECC interventions, with various scenarios: applying fluorides (water fluoridation and FV), limiting cariogenic bacterial transmission from mothers to children (xylitol), using xylitol directly with children, clinical treatment, motivational interviewing, and	Many interventions were compared using modelling. See above.

First author (year of publication), country	Aim of study	Type of economic evaluation	Participants' age / Number of participants (within 2-5 y.o. range)	Participant description	Setting	Intervention(s)	Comparator(s)
						combinations of these.	
Jokela (2003), Finland	To assess the time and costs of a risk-based caries prevention programme compared with conventional prevention.	Cost analysis	2 y.o. children: Risk-based prevention group (n=299) in one municipal health centre, and routine prevention group (n=226) in another municipal health centre in a different town.	2 y.o. children residing in Korpilahti and Saarijarvi, born in 1987 or 1988 (followed for 3 years).	Municipal health centre	Risk-based caries prevention programme: 1) Low risk group: health education for parents; 2) Medium risk: fluoride varnish twice per year; 3) High risk: chlorhexidine and/or fluoride varnish every 3rd month.	Routine prevention group: children received prevention and restorative treatment when the examining dentist considered it necessary on the basis of clinical information.
Jong (1968), USA	A study of the cost and utilization of dental services under a governmentally financed programme of screening, referral, and treatment for economically deprived preschool children.	Cost analysis	4-6 year old preschoolers (n=1303)	Head Start participants aged 4-6 years (economically deprived)	Dental practice **[However, it is unclear in which setting the dental screenings were conducted]**	Dental screening, prophylaxis, treatment with topically applied fluoride solutions (1303 children). Also, for a sub-set of 161 children data on service utilisation were obtained. Out of these, further dental treatment was costed for 158 children (costs mentioned were: dental examination, restorations, local anaesthesia, single tooth extraction and pulpotomy), classified as treatment completed, treatment started but not completed and no	No comparator

First author (year of publication), country	Aim of study	Type of economic evaluation	Participants' age / Number of participants (within 2-5 y.o. range)	Participant description	Setting	Intervention(s)	Comparator(s)
						treatment rendered.	
Kaakko (2002), USA	(1) To assess the effect of the Access to Baby and Child Dentistry (ABCD) programme (in rural Stevens County, Washington, USA) on children's utilization of dental services, (2) To assess the oral health effects of the programme, (3) To determine the average programme expenditures per child.	Cost analysis	Aged 1–4 years. ABCD programme (n=216); regular Medicaid (n=221).	Medicaid-enrolled children aged 1–4 years (born between 01/01/1993 and 31/12/1996).	Private dental practices	ABCD-enrolled children received enhanced benefits that included: three fluoride varnish treatments per year, fluoride-releasing glass ionomer materials used as sealants and fillings in primary teeth, and family preventive oral health instruction once per year.	Regular Medicaid programme
Kranz (2014), USA	To compare the association between the provider of preventive services (primary care providers (PCP), dentist, or both) with Medicaid-enrolled children before their third birthday and subsequent dental caries-related treatment (CRT) and CRT payment.	Cost analysis	3 to 5 yr. 93,986 child-year observations for 41,453 children aged 3 to 5 yr.	Children meeting the following criteria were included: enrolled in Medicaid before 1 yr of age, enrolled for at least 12 mo before their third birthday, and enrolled for at least 7 mo following their third birthday. Children with > 1 visit to PCPs, dentists, or both before their third birthday were included.	Primary care providers, private dental practices, hospitals	Preventive oral health services provided before child's third birthday by either: a) non-dental primary care providers (PCP) - clinical oral evaluation and topical fluoride treatment; b) by dentist - comprehensive or periodic evaluation with fluoride; or c) by both (PCP and dentist).	See Interventions above.
Lewis (1972), Canada	To investigate how dental treatment requirements varied in 1,741 five-y.o. children, depending on	Cost analysis	Mean age ± SD: 5.5 ± 0.6 years (n=1741)	Kindergarten children, who received complete dental treatment.	School	Artificial water fluoridation: 6 study groups based on different lengths of	See Interventions above.

First author (year of publication), country	Aim of study	Type of economic evaluation	Participants' age / Number of participants (within 2-5 y.o. range)	Participant description	Setting	Intervention(s)	Comparator(s)
	their age at the start of water fluoridation in Metropolitan Toronto.			They were from 20 randomly selected schools and have resided since birth in Metropolitan Toronto. **[It looks like there were several (4?) staggered yearly intakes of 5-y.o., which produced an overall study population of varying F exposure. But it's not described clearly in the paper.]**		exposure to fluoride in water.	
Lewis (1977), Canada	To demonstrate the feasibility of providing free dental care to preschool children using private practice facilities, and to collect information which could assist in the development of such a programme on a province-wide basis.	Cost analysis	3 y.o. (n=1775)	Selected from lists of 2- and 3-y.o. children based on 1970 and 1971 Provincial assessment Roles for Waterloo County (Canada).	Community dental clinic (Health Unit) and private dental practices	Preventive (fluoride varnish, prophylaxis and a dental health lesson) and diagnostic dental care only (dental examination, bitewing radiographs) - study Group 3; or complete dental care: preventive, diagnostic and restorative (Groups 1 and 2) was available to children free of charge.	Preventive and diagnostic dental care only *vs* Complete dental care (preventive, diagnostic and restorative)
Pashaev (1982), USSR / Turkmenistan	To evaluate cost effectiveness of caries reduction programme that used three fluoride mediums: fluoride varnish, fluoride liquid	Cost analysis	Age range: 2-11 yr. Intervention group: 495 children of	**[Not explicitly stated but can be assumed]** Children attending dental practices in the city of Ashgabat,	**[Not explicitly stated but can be assumed]** Dental practices	Fluoride drops (2-4 y.o.) and fluoride varnish (5-6 y.o.). Also fluoride tablets for older children (10-11 years)	Children who didn't receive fluoride in any form.

First author (year of publication), country	Aim of study	Type of economic evaluation	Participants' age / Number of participants (within 2-5 y.o. range)	Participant description	Setting	Intervention(s)	Comparator(s)
	("Vitaftor") for oral administration and fluoride pills, aimed at child population of Ashgabat (Turkmenistan/USSR).		preschool and primary school age. Control: 628 children.	Turkmenistan/USSR.			
Potapova (1977), USSR / Russia	To report the results of a longitudinal study on caries prevention effects of artificial water fluoridation and to conduct a cost-effectiveness analysis of this intervention.	Cost analysis for 2-7 y.o., but CBA for the all ages analysis, 2-16 y.o. (not presented in this table).	Age range: 2-16 yr. Not clearly reported: 1302 children of preschool ages (2-7 yr) participated in 1966 (before the start of water fluoridation).	Children attending preschool establishments and schools, who were included into a nursery- or school-based dental treatment programme in a town of Monchegorsk, Russia/USSR (overall 94-96% of the school children population participated in this programme).	Preschool establishments and schools	Artificial water fluoridation	Data for the periods before the start of water fluoridation and for early years of fluoridation.
Rugg-Gunn (1977), UK	To assess the effect of water fluoridation on the caries experience in an urban and rural communities. To calculate cost of dental treatment, according to the NHS scale of fees.	Cost analysis	Mean age at dental examination: 5y. 8mo. and 5y. 7mo., in various sub-groups. 771 in total: 438 in F urban setting; 132 in Non-F urban, 93 in F rural and 108 in Non-F	Caucasian 5 y.o. children attending primary schools in Newcastle upon Tyne and Northumberland (UK), which included urban and rural areas; continuously residing in a respective area from birth. Schools within Newcastle	Primary school	Artificially fluoridated (urban and rural) and non-fluoridated (urban and rural) areas	See "Interventions" above.

First author (year of publication), country	Aim of study	Type of economic evaluation	Participants' age / Number of participants (within 2-5 y.o. range)	Participant description	Setting	Intervention(s)	Comparator(s)
			rural	(fluoridated urban area) were stratified on school type: "social priority" and "ordinary".			
Savage (2004), USA	To determine the effects of early preventive dental visits on subsequent utilization and costs of dental services among preschool-aged children.	Cost analysis	0 y.o. at baseline, birth cohort (n=9204)	Medicaid-enrolled children born in 1992 continuously enrolled for 5 years. Entered the study at birth, followed up until 5y.o.	Data from 4 administrative datasets. Dental claims data are from dental practices and hospitals.	Age at the first preventive dental visit (preventive visit claim): under 1 year, 1 to 2 years, 2 to 3 years, 3 to 4 years, and 4 to 5 years. **[Not stated what exactly was included under "preventive dental visit"]**	No comparator.
Trubman (1991), USA	To calculate treatment costs for restorations and/or extractions for preschool children residing in fluoride-adequate and fluoride-inadequate areas.	Cost analysis	Children aged 3 to 6 yr. F-adequate area: 192 aged 3-4 yr. and 370 aged 5-6 yr.; F-inadequate area: 227 aged 3-4 yr. and 143 aged 5-6 yr.	Child participants of Mississippi Head Start programme, from low-income families, an overwhelming majority were black. Almost all of them were life-long residents of a respective area.	Not described where the dental examination took place.	Residents of fluoride-adequate areas**. [Not clear if it was natural fluoride or artificially fluoridated.]**	Residents of fluoride-inadequate areas.
Wennhall (2010), Sweden **[In combination with Wennhall,**	Tto calculate the total and the net costs per child included in a 3-year caries preventive programme for preschool children and to make estimates of expected lowest and highest costs	Cost analysis	2 y.o. at baseline. 804 in intervention group at the start. End of study (at 5 y.o.):	Most of the children were immigrants, and 94%spoke languages other than Swedish at home.	Community, dental practice, child health centre	Diet information and toothbrushing training provided to parents at regular intervals at an outreach facility; also free fluoride tablets, free toothbrushes and fluoride toothpaste (at a	No intervention.

First author (year of publication), country	Aim of study	Type of economic evaluation	Participants' age / Number of participants (within 2-5 y.o. range)	Participant description	Setting	Intervention(s)	Comparator(s)
2008]	in a sensitivity analysis.		651 remained in intervention group and 201 in control group. **[From Wennhall, 2008]**			discounted price) were provided.	
Zavras (2000), USA	To estimate an economic model for the potential cost impact of microbiological screening of toddlers for caries risk compared to the traditional method of managing paediatric caries.	Cost analysis	1 to 3 years (n=1,180)	All new patients presenting to a regional community-based private paediatric dental practice between 1988 and 1995 were cultured for salivary mutans streptococci levels. Only the data for the age group 1 to 3 years is included into this study.	Regional community-based private paediatric dental practice	Microbiological screening (mutans streptococci) of toddlers aged 1-3 years for caries risk.	No screening.

Appendix 6 Partial EEs: Methods, results and authors' conclusions

Study first author (year of publication), country	**EE methods**	**Results (**outline, including sensitivity analysis)	**Authors' conclusions**
Anopa (2015), UK	Cost calculations. Estimated costs of the nursery toothbrushing programme in 2011/12 were requested from all Scottish Health Boards. Unit costs of a filled, extracted and decayed primary tooth were calculated using verifiable sources of information. Total costs associated with dental treatments were estimated for the period from 1999/00 to 2009/10. These costs were based on the unit costs above and using the data of the National Dental Inspection Programme and then extrapolated to the population level. Expected cost savings were calculated for each of the subsequent years in comparison with the 2001/02 dental treatment costs	The estimated cost of the nursery toothbrushing programme in Scotland was £1,762,621 per year. The estimated cost of dental treatments in the baseline year 2001/02 was £8,766,297, while in 2009/10 it was £4,035,200. In 2002/03 the costs of dental treatments increased by £213,380 (2.4%). In the following years the costs decreased dramatically with the estimated annual savings ranging from £1,217,255 in 2003/04 (13.9% of costs in 2001/02) to £4,731,097 in 2009/10 (54.0%). Sensitivity analysis: in 2001/02 the 'low GA cost' scenario total cost of dental treatments was £5,410,531 and in case of 'high GA cost' it was £18,325,312. In 2009/10 the costs in these scenarios were £2,501,964 and £8,402,746 respectively. Population standardised analysis by deprivation groups showed that the largest decrease in modelled costs was for the most deprived cohort of children.	The NHS costs associated with the dental treatments for five-year-old children decreased over time. In the eighth year of the toothbrushing programme the expected savings were more than two and a half times the costs of the programme implementation. The toothbrushing programme represents an example of a preventative spend and a 'win win' scenario of both reduced costs and health gains in child oral health outcomes. A population standardised analysis of hypothetical cohorts of 1000 children per Depcat showed that the largest decrease in costs and associated dental health gain occurred in the cohorts of children within the highest deprivation categories.
Ast (1970), USA	Groups of 5- and 6-y.o. children residing in the poorest socioeconomic areas in a city with fluoridated water supply and in a city with a non-fluoridated supply were selected for study. At the time a child was admitted to the study, all accumulated carious defects were corrected, then annual routine incremental care was given each year. All treatment was provided in a dental trailer staffed by a full-time dentist and dental assistant. Services rendered included all those usually provided in a dental office, except for prosthetic or orthodontic services. A detailed record was kept of each dental examination, including the types of services rendered.	41% of children in the fluoridated area (F) were caries free at baseline, compared with 17% in the non-fluoridated area (NF). At both the initial examination and in each incremental year the NF children required more restorations and extractions that F children. Both incremental and cumulative costs were twice as high for NF children, and chair time was more than 1.5 times greater.	Fluoridated water and regular periodic dental care starting early in life are essential for reducing the hazard of tooth loss and for economic reasons.

Study first author (year of publication), country	**EE methods**	**Results (**outline, including sensitivity analysis)	**Authors' conclusions**
	The amount of chair time required was also recorded.		
Buckingham (2017), UK	Simple cost calculations. The programme was costed as a whole, rather than just the delivery of FVAs. Programme costs included: clinical staff, oral health promotion staff; administrative staff; non-pay costs (travel, office supplies, oral health improvement resources); delivery of FVA (consumables and equipment).	The percentage of children with dental decay experience went up in all areas except for one site, where it stayed at the same level. There were larger increases in the cohorts with older children. Staff costs made up the bulk of the total costs. The total cost of delivering the programme (engagement with sites, securing consent, recording and updating medical history, dental screening, delivering oral health education and fluoride varnish applications) to the 189 school children (aged 4-7 years) enrolled at one of the study sites was £13,500 per year (£71 per child). When including just the 153 children who received at least two FVAs per year over the three-year period, the programme cost £88 per child.	Authors' experience indicates that it is feasible to carry out fluoride varnish applications in a community setting. However, intensive efforts were needed to secure and maintain participation, making this an expensive intervention which may be difficult to sustain for the long term. There was an increase in the number of children attending for dental care and receiving treatment but also an increase in dental decay experience. [I.e. baseline compared with the end of the study.]

Study first author (year of publication), country	**EE methods**	**Results (**outline, including sensitivity analysis)	**Authors' conclusions**
Chen (2009), Taiwan	A difference-in-difference methodology or a pre–post design with a control group was used. The change (or difference) in utilization of dental services and costs before and after fluoride gel application for the study group was compared to the change over the same period for the control group. The costs were the aggregate of all itemized charges for services and disposables billed to the Bureau of National Health Insurance. Dental services utilization and costs were categorized according to three conditions: treatment procedures for dental caries, treatment procedure for pulpitis and treatment for other conditions.	Prior to fluoride gel application, the average cost of treating caries per person/year in the study group was higher than that in the control group (NT$ 1512 vs. NT$ 520, respectively), but this pattern was reversed after fluoride gel application (NT$ 2366 and NT$ 3466 in the study and control groups, respectively), and the growth in costs associated with dental caries was smaller for the study group than for the control group (NT$ 854 compared to NT$ 2946, respectively). Prior to fluoride gel application, the average cost of dental-visits for all conditions per person/year was higher for the study group (NT$ 1945) than for the control group (NT$ 668), but this reversed after fluoride gel application (NT$ 3310 vs. NT$ 4730 for the study and control groups, respectively). The growth in costs associated with dental-visits for all conditions was likewise smaller for the study than for the control group (NT$ 1365 compared to NT$ 4062). NT$ 2092, NT$ 532, and NT$ 2697 were saved on caries treatment, pulpitis treatment and total dental costs, respectively, for each preschool child per year in the study group. Regression analysis: fluoride application was associated with the reductions of 1.42, 0.43, and 1.92 in treatments for dental caries, pulpitis and total dental utilization, respectively. In addition, age, urbanization level, and geographic region were significantly related to total dental service utilization.	Fluoride gel application is associated with a slower rate of growth in the number of visits for the treatment of dental disease and lower dental care expenditures for preschool children.

Study first author (year of publication), country	**EE methods**	**Results (**outline, including sensitivity analysis)	**Authors' conclusions**
Dowell (1976), UK	Fluoridation costs data were received from Wessex Water Authority. The mean cost of treating caries in the deciduous and permanent dentition has been calculated from the reports of the Dental Estimates Board (general dental services) and estimates of the cost of the community dental service – all calculations relate to England. The cost of all conservative work, extractions, anaesthetics and dentures was included for children. Then the reduction in the need for treatment (due to fluoridated water supply) was estimated, based on previously reported data from other countries. It was estimated that the treatment of caries would be reduced by approx. 55%. Further, these estimates were applied to a standard population of 100,000 (stratified by age according to the population of England), with a final aim of estimating annual savings in treatment of caries (discounted savings and total present value of saving) over 30 years, and, ultimately to calculate the "economic cost", which is the annual cost per person of fluoridation at which the present values of the theoretical savings and of the expenditure are equal.	[Only results related to 3-4 y.o. are included here]: Mean annual cost of deciduous teeth treatment = £0.96; mean annual savings in caries treatment costs (due to lifetime experience of fluoride) = £0.53; annual savings in caries treatment costs for standard population, for 3,095 children of 3-4 y. = £1,640.	The overall study conclusion: Sources of supply with yields of 1 million gallons per day or more are likely to be economic to fluoridate but very small sources may be too expensive to justify the installation of a plant.

Study first author (year of publication), country	**EE methods**	**Results (**outline, including sensitivity analysis)	**Authors' conclusions**
Edelstein (2015), USA	System dynamics modelling was applied to the New York State Medicaid population of young children to compare potential outcomes of 9 preventive interventions. (System dynamics modelling is a computer simulation technique that allows the user to anticipate the effect of interventions in complex situations with interdependent variables.) Model parameters were based on numerous previous publications sand other verifiable sources of information.	Model simulations help project 10-year disease reductions and net savings from water fluoridation, motivational interviewing, and fluoride toothpaste. Interventions requiring health professionals cost more than they save. Interventions that target children at high risk, begin early, and combine multiple strategies hold greatest potential. Defluoridating New York City would increase disease and costs dramatically.	The variety of population-level and individual-level interventions available to control ECC differ substantially in their capacity to improve children's oral health and reduce state Medicaid expenditures.
Fidler (1977), UK	The treatment and cost comparisons were made based on the data on individuals seeking treatment between Dec 1973 and March 1974. The treatment and cost data are from an NHS form completed by the dentist at the time of accepting the patient (FP17 form). Costs are based on the Statement of Dental Remuneration in force at that time.	2-4 y.o. children in Watford (fluoridated area) had on average 0.20 (SD=0.65) of cavities restored (a single surface cavity), in comparison with 0.35 (0.87) cavities restored in the non-fluoridated areas. Average cost of single surface restorations was £0.32 in the non-fluoridated areas and £0.18 in Watford (43.7% reduction in the average cost). In regard to "amalgam restorations, more than one surface", the mean number of treatments for 2-4 y.o. children in Watford was 0.09 (0.45) while in the non-fluoridated areas it was 0.16 (0.60). The average cost of amalgam restorations, more than one surface was £0.21 in the non-fluoridated areas and £0.12 in Watford (42.8% reduction in the average cost).	Despite the possibility of underestimating the effectiveness of fluoridation, this paper demonstrates that there are considerable savings in treatment costs where fluoridation has been introduced.

Study first author (year of publication), country	**EE methods**	**Results (**outline, including sensitivity analysis)	**Authors' conclusions**
Gisselsson (1994), Sweden	Time of treatment by a dental nurse in the gel groups was recorded during the study. The time required for the regular dental treatment was obtained from the annual record of each child. The average staff costs were calculated for the dental nurse in the study groups and for a team of one dentist and one chairside assistant for regular dental treatments. [Source of these data was not indicated.]	At the end of the study children in the chlorhexidine group had a deft (SD) of 1,98 (2.57), children in placebo group had deft = 2.43 (2.80) and those in the control group had deft = 3.03 (3.51). The professional flossing-gel programme required on average 130 min (13 x 10 min) per child during the 3-year period. The average cost of a dental nurse was 117 SEK per hour. The average cost for the team (of one dentist and one chairside assistant) was 370 SEK per hour. During the 3 years of the study duration a child in the chlorhexidine group on average required 134 min of the team's time and 130 min of the nurse's time (costing 826 SEK and 245 SEK, respectively). A child in the control group required 180 min of the team's time and 1 min of the nurse's time (costing 1,110 SEK and 2 SEK, respectively). Cost of the gel programme was calculated as 254-2 = 252 SEK, while the dental team costs were 284 SEK higher in the control group in comparison with the gel group. The fact that the children participating in the chlorhexidine gel programme and their parents had to spend more time for their visits to the clinic than those in the control group was disregarded in the economic analysis.	A cost analysis based on the total treatment in minutes showed a small gain for the flossing programme. The results indicate that professional application 4 times a year of chlorhexidine gel in combination with dental flossing has caries-reducing effect on approximal caries in primary teeth.

Study first author (year of publication), country	**EE methods**	**Results (**outline, including sensitivity analysis)	**Authors' conclusions**
Hawkins (2004), Canada	Simple cost calculations. SPSS 10.1 and STATA were used. STATA's robust estimator of variance and cluster options were used in linear and logistic regression analyses to account for the design effect of different hygienists providing the PATFs. Children received from dental hygienists either fluoride foam applied in trays or fluoride varnish painted on tooth surfaces. An observer recorded the time taken to perform the application, adverse outcomes, and the satisfaction of children with the treatment. The variable "time" was entered in minutes and rounded to the nearest quarter-minute. Cost per application was the sum of the cost of labour to complete an application and the cost of supplies per application. The costs of supplies used in both techniques (e.g., saliva ejectors) were not included in the estimate.	The varnish technique took significantly less time compared to foam (5.81 vs 7.86 minutes; P<.0001). Significant differences between procedure times were found in all age groups, but the largest difference was for children aged 3-6years (5.22 vs 8.61 minutes; p<.0001). Signs of gagging were observed in a lower proportion of participants who received varnish (3.8% vs 15.1 %; p<.01), and this difference was largest for children aged 3-6 years (2.6% vs 29.7%; p<.01). The cost per varnish application, for children aged 3-6 years, was substantially less after labour costs were considered ($3.43 vs $4.43). Mean time of procedure (SD) for the 3-6 y.o. sub-group were, in minutes: 8.61 (2.30) for foam and 5.22 (1.21) for varnish (p<.0001). The cost per application for 3-6 y.o. patients was 4.43 for foam and 3.43 for varnish.	Varnish applications were found to take less time and resulted in fewer signs of discomfort. These results support using fluoride varnish in caries prevention programmes, especially for younger children. Fluoride varnish is safe and easy to apply, fluoride ingestion is minimal, and this application method has greater patient acceptability. Treatment can be provided at a lower cost due to the reduced application time. For these reasons, it is more appropriate to use fluoride varnish in public health settings when treating high caries-risk children.
Hirsch (2012), USA	A system dynamics model was formulated to assess and compare ECC interventions for benefits and costs among children aged 0-5 years in Colorado. The basic model structure was developed by a work group of paediatric medical, dental, and public health experts. It separates children by age (0-6, 7-24, and 25-72 mo.) and risk of developing ECC (low, moderate, high), using household income as a surrogate for risk. Multiple data sources were used to quantify the model and the effects of simulated interventions.	The model projected 10-year intervention costs ranging from $6 million to $245 million and relative reductions in cavity prevalence ranging from none to 79.1% from the baseline. Interventions targeting the youngest children take 2 to 4 years longer to affect the entire population of preschool-age children but ultimately exert a greater benefit in reducing ECC; interventions targeting the highest-risk children provide the greatest return on investment, and combined interventions that target ECC at several stages of its natural history have the greatest potential for cavity reduction. Some interventions save more in dental repair than their cost; all produce substantial reductions in repair cost.	By using data relevant to any geographic area, the developed system model can provide policy makers with information to maximize the return on public health and clinical care investments.

Study first author (year of publication), country	**EE methods**	**Results (**outline, including sensitivity analysis)	**Authors' conclusions**
Jokela (2003), Finland	For every child in the high-risk or routine group the amount of time spent by dental staff was recorded in minutes in the personal records. Actual running costs of a health centre were used for the analysis. Average staff costs per hour, including costs other than salary (materials and other expenses), were calculated for a dentist+assistant team and a preventive dental assistant. The cost per child for the 3-year follow-up were calculated by multiplying the time spent by the costs per hour of the required personnel.	The total cost of a dentist+assistant team was estimated at 75 €/h, cost of a preventive dental assistant was 30 €/h. The costs per child per 3 years were significantly lower in the risk-based group (54 €) than in the conventional prevention group (69 €). If a dentist with an assistant had done all the work (hypothetical scenario 1), the costs would have been twice as high (134 € for each group). In the hypothetical scenario 2, the mean cost per child in the risk-based prevention group would be 23 € and 47 € for the routine group.	Compared to conventional prevention, the results suggest that risk-based prevention can be effective in reducing both costs and dental caries in preschool children, provided that the screening and preventive measures are delegated to preventive dental assistants.
Jong (1968), USA	Simple cost calculations. Dentists submitted their bills for the children treated to the Health Office of Head Start. The charges were based on the schedule of fees of the Department of Public Welfare of the Commonwealth of Massachusetts (as of 1966): $5.00 for examination; $5.00 for one surface restoration of silver amalgam; $8.00 for a two-surface restoration; $10.00 for three or more surface restoration; $4.00 for local anaesthesia and the extraction of a single tooth; $10.00 for a pulpotomy. At the end of the study records were obtained from the Health Office to determine the cost of treatment (158 children).	Out of a sub-sample of 161 children 50.3% completed treatment, 17.4% received partial treatment and 1.9% (3 children) were lost to follow-up. Further cost analysis of the data of 158 children revealed that: a) the total cost of follow-up was $4957; b) the mean cost per patient in the referral programme was $31.37, range $5.00-$167.00 (mean cost per child receiving partial treatment was $21.43 and cost per child receiving complete treatment was $53.79); c) the children investigated required 459 visits to a dentist or an average of 2.91 visits per child at a cost of $10.80 per visit; d) in addition, the total cost of screening, preventive and referral procedures was $11000 (an average cost of $8.44 per child); e) the additional administrative costs for the follow-up and referral were $2,620 or $4.51 per child.	It appears that a programme which combines the technics of persistent referral and subsidised dental treatment can be successful for an indigent population.

Study first author (year of publication), country	**EE methods**	**Results (**outline, including sensitivity analysis)	**Authors' conclusions**
Kaakko (2002), USA	Medicaid-enrolled children aged 1–4 years were randomly assigned to the ABCD programme (n=216) or to regular benefits (n=221). An outreach worker contacted each ABCD family and provided an orientation. Dental care utilization and expenditures were calculated from claims. A posttest-only design was used to evaluate oral health status. The utilization and expenditure variables were constructed from Medicaid dental claims between 01/02/1997 and 31/07/1999. Expenditures for the dentist certification course and for the outreach effort for the ABCD children after assignment to conditions were obtained from university and state records. These expenditures were added to the average cost per child for dental care in the ABCD group and the number was compared to the cost per child for the Medicaid-enrolled children not in ABCD. For each health outcome that was statistically significant (P<.05), the difference between the average expenditures for the two groups was divided by the difference in the average outcomes in the two groups to obtain the average cost of an additional unit of benefit from the intervention.	An enrolment effect was seen in ABCD, but the difference between groups was not sustained. There was a doubling of utilization between groups for the youngest cohort, while the others showed no differences. In the first year the rate was higher for the entire ABCD group than for the children not in ABCD (34.0% vs 24.7%). 33% of ABCD children (70/212) who had visited the dentist had >1 appointment compared to 21.5% (47/219) for the children not in ABCD who had visited the dentist. There was no overall difference in expenditures, while expenditures for preventive services were greater for ABCD. ABCD children had fewer teeth with initial caries. The mean expenditures for training and outreach were $5.76 for ABCD and $15.72 for non-ABCD per child. For the entire 29-month period, the mean dental care expenditures per child were $181.41 (ABCD) and $192.50 (Medicaid enrolled children not in ABCD). The difference in the average number of initial carious lesions was 0.5. The cost per unit of benefit was determined to be $31.44.	ABCD most benefited the youngest cohort of children and improved health.

Study first author (year of publication), country	**EE methods**	**Results (**outline, including sensitivity analysis)	**Authors' conclusions**
Kranz (2014), USA	A retrospective study of young children enrolled in North Carolina Medicaid during 2000 to 2006. The annual number of CRT and CRT payments per child between the ages of 3 and 5 yr were estimated with a zero-inflated negative binomial regression and a hurdle model, respectively. Models were adjusted for relevant child- and county-level characteristics and used propensity score weighting to address observed confounding.	The data of 41,453 children with > 1 preventive oral health visit from a PCP, dentist, or both before their third birthday were studied. Unadjusted annual mean CRT and payments were lowest among children who had only PCP visits, Mean ± SD (CRT = 0.87 ± 2.96, payment = $172 ± $1,865) and higher among children with only dentist visits (CRT = 1.48 ± 3.17, payment = $234 ± $853) and both PCP and dentist visits (CRT = 1.52 ± 3.48, payment = $273 ± $1,018). Adjusted results indicated that children who had dentist visits (with or without PCP visits) had significantly more CRT and higher CRT payments per year during the ages of 3 and 4 yr than children who had only PCP visits. However, these differences attenuated each year after age 3 yr.	Because of children's increased opportunity to receive multiple visits in medical offices during well-child visits, preventive oral health services provided by PCPs may lead to a greater reduction in CRT than dentist visits alone. This study supports guidelines and reimbursement policies that allow preventive dental visits based on individual needs.
Lewis (1972), Canada	The children were divided into 6 groups according to the exact decimal years between birth and the start of water fluoridation (F): Group A – born over 11 mo. prior to start of F; Group B – born between 11 mo. to 7 mo. to before F (inclusive); Group C – born from 6 mo. before to the day F started; Group D – born the day after F to 9 mo. after; Group E – born 10 mo. to 15 mo. after F; Group E – born from 16 mo. to 28 mo. after F started. Each group from A to F was increasingly exposed to F during primary tooth development and maturation. The data on type of dental care received, mean No of amalgam restorations and mean chair time were collected during the study. Costs were tabulated using the 1967 Ontario Dental Association fee schedule of unit fees and hourly rates.	Group A (shortest F exposure) vs Group F (longest exposure), all are mean values: No of total amalgam restorations – 3.47 vs 1.20; total care costs – $63 vs $31; operative care – $46 vs £14; hourly fee – $40 vs $18; chair time (min) – 91 vs 42.	Saving of over 50% in amalgam restorations, costs and chair time were realised by high F compared to low F exposure groups. The findings suggest that the critical time for exposure to F is during post-natal, pre-eruptive phase of tooth development. The earlier the exposure in this period, the more complete the protection.

Study first author (year of publication), country	**EE methods**	**Results (**outline, including sensitivity analysis)	**Authors' conclusions**
Lewis (1977), Canada	Simple cost calculations. Not much details provided, only mean cost per child and a total for the project's administration and research costs.	Cost per year of providing diagnostic and preventive services only ranged from $13.16 to $18.22 per patient. Mean cost of diagnostic and preventive services only group (Group 3) over the entire course of the project was $41.69. In addition to costs of dental services a total of $70,586 was spent on administration and research over the course of the project (no further specification was provided).	It is feasible for a regional government agency to administer a private practice preschool children's dental care plan.
Pashaev (1982), USSR / Turkmenistan	Simple cost calculations. However, not much detail is provided. An average cost of a dental treatment visit and a fluoride varnish application visit were calculated. The total average costs of dental treatments (excluding orthodontic treatment) and prophylaxis were calculated for 1000 control children and for the children in intervention groups (per 1000 as well), as per treatments requires in the end of the 2-year study period. Then these costs were compared and cost savings were calculated.	The numbers of new carious cavities developed by the end of two years in the intervention groups were lower than in the control group. It was 50.5% lower for the fluoride varnish group (5-6 y.o.) and 33.0% lower for the fluoride liquid group (2-4 y.o.). The costs of dental treatment at the end of the 2-year study period was 535.31 roubles per 1000 children and 598.00 roubles per 1000 children respectively. The average dental treatment costs for the control group was 767.00 roubles per 1000 children. Thus, the cost savings per 1000 children were 231.69 roubles for the fluoride varnish group and 169 roubles for the fluoride liquid group.	The results of the study showed that the fluoride supplements in question were highly effective in preventing dental caries and also cost-effective.
Potapova (1977), USSR / Russia	Simple cost analysis (for preschool ages) and simple cost-benefit analysis for the overall age group (2-16 yrs). Costs of filling materials and dentist's time spent on average for treating one child were calculated. The difference in treatment time required every year (in multiple cross-sectional surveys) meant the dentist's time saved. Annual cost of water fluoridation and average cost per person was calculated (although not much details were provided). Cost/benefit ratio was calculated by comparing the cost of water fluoridation with the cost savings resulting	In 1976 mean df in preschoolers (2-7 y.o.) decreased by 26% compared with the 1966 rate (pre-fluoridation), and by 21.7% in comparison with 1971 (early fluoridation period). In 1971 the average time required to perform dental treatment per preschool child (2-7 y.o.) was 129.8 min, while in 1976 it was 67.6 min. The total cost of dental treatment per preschool child decreased from 9.64 roubles to 4.91 roubles, respectively. [Mean df and cost data by single year of age, as well as data for school-age children (7-16 yr) are also reported in the paper.] Cost/benefit ratio was 1:5.9 in 1975 and 1:6.2 in 1976 (for all child ages combined, 2-16 y.o.).	The results of this study show that artificial water fluoridation is an effective and cost-effective caries prevention measure in an area with high childhood caries rates.

Study first author (year of publication), country	**EE methods**	**Results (**outline, including sensitivity analysis)	**Authors' conclusions**
	from fewer dental treatments required.		
Rugg-Gunn (1977), UK	The cost of dental treatment was based on the NHS scale of fees 1976. Costs of dental treatment already completed included fillings, extractions, GA (from parental questionnaire), while treatment required included fillings, discings, extractions, GA and gingival treatment. A number of assumptions were used: deciduous incisors would be disced rather than filled; all extractions would be carried out in one appointment; if 1 or 2 teeth were to be extracted, LA would be used, if more than 2 teeth were to be extracted, GA would be used; a "scale and polish" fee would be incurred if a child had 1 or more gingival site scores of 3 on the G.I. scale.	Dental caries was 57% (3.5 teeth per child) lower in F urban area and 67% (4.1 teeth per child) lower in F rural area compared with the corresponding Non-F areas. Costs per child. a) Treatment already completed: F urban (ordinary) = £1.41; F urban (social priority) = £1.16; Non-F urban = £1.81; F rural = £1.27; Non-F rural = £1.63. b) Treatment still required: F urban (ordinary) = £2.69; F urban (social priority) = £2.96; Non-F urban = £7.62; F rural = £1.93; Non-F rural = £7.89. The cost of treatment already completed was lower in the F areas: by 36% (£0.65 per child) in F urban and by 22% (£0.36 per child) in F rural. The difference between F and Non-F areas was more marked for costs of treatment still required. This difference was nearly £6 (76%) in the rural communities and £4.66 (61%) for the urban communities. With regards to treatment already completed, the proportion spent on GA and extractions, as opposed to fillings, was higher in Non-F rather than F areas: for F urban (social priority) it was 66%, F urban (ordinary) = 42%; Non-F urban = 97%; F rural = 34% and Non-F rural = 75%. **[No individual costs by component were reported. Only the cumulative average cost per child.]**	The authors concluded that fluoridation was substantially improving the dental health of young children in the Newcastle / Northumberland area.

Study first author (year of publication), country	**EE methods**	**Results (**outline, including sensitivity analysis)	**Authors' conclusions**
Savage (2004), USA	Four administrative datasets were used: 1) composite birth records from the 1992 calendar year, 2) individual Medicaid-eligibility files for all children born in 1992 and enrolled continuously in the Medicaid programme from 1992 to 1997, 3) Medicaid dental claims data covering 1992–1997, and 4) the Area Resource File. The relationship of early preventive dental visits to subsequent use and costs was determined by using various multiple regression analyses with control variables. Probit analyses (logistic regression) was used for each type of oral health care service used. The type of service was classified as preventive, restorative, or emergency. A multivariate liner regression model was used for dentally related costs.	Twenty-three children had their first preventive dental visit before 1 year of age, 249 between 1 and 2 years, 465 between 2 and 3 years, 915 between 3 and 4 years, and 823 between 4 and 5 years. The age at the first preventive dental visit had a significant positive effect on dentally related expenditures, with the average dentally related costs being less for children who received earlier preventive care. The average dentally related cost per child during the 5 years of the study was $447 for those who used dental services. The average dentally related costs per child according to age at the first preventive visit were as follows: before age 1, $262; age 1 to 2, $339; age 2 to 3, $449; age 3 to 4, $492; age 4 to 5, $546. Minority children were less likely to have subsequent preventive visits, restorative visits, or emergency visits, whereas children from counties with greater number of dentists per 10 000 population were more likely to have subsequent dental visits of all types.	Our results should be interpreted cautiously, because of the potential for selection bias; however, we concluded that preschool-aged, Medicaid-enrolled children who had an early preventive dental visit were more likely to use subsequent preventive services and experience lower dentally related costs. In addition, children from racial minority groups had significantly more difficulty in finding access to dental care, as did those in counties with fewer dentists per population.
Trubman (1991), USA	A random cluster design was employed to obtain a 10% representative sample of Mississippi Head Start children aged 3-6 years for dental examination. Subgroups from F-adequate (n=562) and F-inadequate (n=370) areas were selected. Dental caries experience of primary teeth was determined by visual examination. Cost estimates were made for each age-group by applying the Mississippi EPSDT/Medicaid fee schedule to the type of treatment needed. For four and five-surface lesions, it was assumed that treatment would require pulpotomies and stainless steel crowns.	In each age-group, children from F-inadequate areas had a significantly higher No of carious teeth that children from F-adequate areas. There were significant differences between the children from the two types of areas in relation to most types of treatment needs, except for teeth indicated for extraction and for 5-surface lesions (in the 3-4 y.o. group only). Mean costs of treating carious primary teeth per child were: a) F-inadequate areas: $38.33 per 3-4 y.o. child and $56.01 per 5-6y.o. child; b) F-adequate areas: $8.24 per 3-4 y.o. child (or 21.5% of the cost per child in F-inadequate areas) and $15.92 per 5-6y.o. child (or 28.4% of the cost per child in F-inadequate areas). **[Not much detail is reported with regards to the itemisation of costs. Only mean costs per child / per F-area type / per age-group was reported.]**	No conclusions were drawn by the authors in this paper.

Study first author (year of publication), country	**EE methods**	**Results (**outline, including sensitivity analysis)	**Authors' conclusions**
Wennhall (2010), Sweden	The direct costs for prevention and dental treatment were applied retrospectively to a comprehensive oral health outreach project for preschool children conducted in a low-socioeconomic multi-cultural urban area. The outcome was compared with historical controls from the same area with conventional dental care. The cost per minute for the various dental professions was added to the cost of materials, rental facilities and equipment based on accounting data. The cost for fillings was deducted from a specified per diem list. Overhead costs were assumed to correspond to 50% of salaries and all costs were calculated as net present value per participating child in the programme and expressed in Euro.	A total mean cost of per included child in the 3-year programme was estimated at 310 Euro (net present value). Half of the costs were attributed to the first year of the programme and the costs of manpower constituted 45% of the total costs. In order to estimate the net costs, the costs of the conventional care in the reference group and the benefit of avoided fillings in the intervention group were subtracted from the total costs. The estimated cost per child for dental care in the reference group up to 5 year of age was 96 Euro and the net present revenue for an average of three avoided fillings per child was estimated to 184 Euro (67.15 Euro per filling). Consequently, the expected net cost of the preventive programme was 30 Euro per included child in the project. In the sensitivity analysis, the 95% confidence interval of the risk reduction was used to estimate a minimum and maximum outcome of the programme. Ranging from defs 1.66 to 4.34, the net costs of a minimum outcome was 109 Euro per child. At a maximum defs outcome however, a net gain of 61 Euro per child was to be expected.	This retrospective cost analysis of a 3-year preventive programme directed to preschool children living in a low-socioeconomic multi-cultural area indicated a net cost of approximately 30 Euro per child up to the age of 5 years. Continuing follow-ups in the permanent dentition are required in order to investigate the long-term benefit of such a preventive programme.

Study first author (year of publication), country	**EE methods**	**Results (**outline, including sensitivity analysis)	**Authors' conclusions**
Zavras (2000), USA	Potential cost savings were calculated based on screening test properties (sensitivity and specificity) derived from a population of 1,180 children aged 1 to 3 years with a caries prevalence of 15%. An algorithm was then developed to allocate prevalent and anticipate incident caries, treatment effectiveness assumptions, and existing regional treatment costs. Treatment costs used in the model reflected common fees for New England, those accepted by dental insurers as usual, customary, and reasonable. **[Limited information. No exact sources were cited.]** In the case of no screening, expected costs reflect the sum of each disease pattern's likelihood of occurring multiplied by its associated treatment costs. Costs were calculated for the treatment of baby bottle tooth decay (BBTD), "other decay," and "incident decay." When screening is done, expected costs reflect the sum of each disease pattern's likelihood of occurring multiplied by its associated treatment costs, the cost of the test, and costs associated with treating decay, because of a false-positive or false-negative test.	The cost analysis model conservatively predicts savings of 7.3 percent from screening and early intervention. Cumulative dental treatment costs for a child at age 4 years are $367.90 if the child has been screened and $396.70 otherwise (an expected savings of $28.80 per child). The largest component of a screened case is for false negatives ($124.50) because the cost of treatment will be the same as for a child who is not screened. The model further predicts that cost savings increase significantly as caries prevalence increases.	Microbiologic risk assessment for paediatric caries may be an example of a preventive public health screening technique that results in both clinical benefits and cost savings. If the model is validated by randomized clinical trials, microbiologic screening could be used by paediatric primary care providers to identify toddlers who require early referral to dentists for further risk assessment and early caries management

Appendix 7 Full EEs: Study aim, participants and settings description, interventions and comparators

Study first author (year of publication), country	Aim of study	Type of economic evaluation	Participants' age / Number of participants (within 2-5 y.o. range)	Participant description	Setting	Intervention(s)	Comparator(s)
Donaldson (1986), UK	To compare the clinical and economic effects of a programme of preventive dentistry for children in an inner-city health centre with those for traditional restorative care.	CEA	a) aged 0-2 years at entry (n = 73), b) aged 3-6 (n = 88). 161 children who entered the programme in 1978 and attended continuously for a period of 4 years: a) aged 0-2 years at entry (n = 73), b) aged 3-6 (n = 88).	Participants were drawn primarily from the general medical practices associated with a health centre or were patients of the centre's general dental practices.	Health centre / general dental practice	Personal **health education, fluoride drops / tablets, fluoride gel applications and pit and fissure sealing** (in a health centre).	The costs of restoring the carious surfaces that would have been expected to occur without the prevention programme were estimated by multiplying the annual reductions in dmfs and DMFS by the appropriate fee for an amalgam filling in a single surface cavity.
Widenheim (1991), Sweden	To assess restorative care, approximal caries, and cost-effectiveness in children at the ages of 8 and 17 yr in relation to NaF tablet intake between 0.5 yr. and 7 yr of age.	CEA	No baseline age reported. Participants were retrospectively divided (based on an interview) into six groups, according to decreasing NaF intake pattern. Overall, participants had an opportunity to consume NaF tablets between the ages 0.5 yr. to 7 yr. n=304 (of these, 64 were in the longest regular NaF consumption group and 90 in the non-consumers group)	Subjects born in 1967 had resided from birth in Lund, Sweden (with F content in water of 0.2 ppm).	Public Dental Service clinics	**Sodium fluoride (NaF) tablets**. Plus annual dental care from 3 y.o., **basic preventive programme**: **FVA** once a year (including weekly mouth rinsing with NaF solution from 6 y.o.), and **fluoride varnish** once a year. High caries risk individuals received **tailored preventive care**. Assumed that all children used **fluoride toothpaste** daily at home from at least 4 y.o.	Non-consumers of NaF tablets.

Study first author (year of publication), country	**Aim of study**	**Type of economic evaluation**	**Participants' age / Number of participants (within 2-5 y.o. range)**	**Participant description**	**Setting**	**Intervention(s)**	**Comparator(s)**
Ramos-Gomez (1999), USA	To determines the cost-effectiveness of 3 successively more complete levels of preventive intervention (minimal, intermediate, and comprehensive) in treating dental caries in disadvantaged children up to 6 years of age.	CEA	1 y.o. at baseline followed up for five years (hypothetical cohort). Not stated (looks like all calculations were on a child level and a tooth surface level basis)	Hypothetical cohort of disadvantaged children	Dental practice	3 preventive interventions incorporating successive components: minimal (**risk assessment** and **FVA,** 6-monthly), intermediate (minimal + parental counselling / **OH education**, child age specific), and comprehensive (intermediate + **outreach, telephone and personal prompts**, and **incentives**).	Absence of any preventive intervention
Davies (2003), UK	To assess the cost-effectiveness of a postal toothpaste programme to prevent caries in 5-year-old children in the north-west of England.	CEA	Birth cohorts of children followed up from 12 mo to 5 y. 5,344 completed the study.	Children living in deprived, non-fluoridated areas of the North West of England.	Home toothbrushing	Postal programme: **fluoride toothpaste** and **information leaflet** encouraging twice daily supervised TB (x 4 times a year) and **toothbrush** (once a year). Run for 4 years: from 1 y.o. to 5 y.o.	"Do nothing"
Kowash (2006), UK	To investigate whether early or regular preventive dental visit (PDV) reduces restorative or emergency dental care and costs for low-income children.	CBA and CEA	Approx 8 mo at recruitment; At baseline dental examination: Mean = 11.4 mo (SD = 3.4 mo). 179 in intervention groups (at the end of 3-year study, aged 3y): Group A=45, B=47, C=51, D=36; and 55 in control group. **(Data from**	Chn born between 1 Jan - 30 Sept 1995, resident in low socio-economic/high caries suburbs of Leeds (randomly selected).	Family homes	Group A: received **dental health education** (DHE) focused on **diet** and briefly on oral hygiene. Group B: **oral hygiene** instruction (with fluoride toothpaste) and briefly on diet. Group C: DHE equally balanced between **diet and oral hygiene**. Each mother was given DHE using a structured interview and counselling for at least 15 minutes in her own home every 3 months for the first 2 years of the study and twice a year in	Group E (control): were only examined at 3 years of age for dental caries and oral hygiene in nursery school.

Study first author (year of publication), country	Aim of study	Type of economic evaluation	Participants' age / Number of participants (within 2-5 y.o. range)	Participant description	Setting	Intervention(s)	Comparator(s)
			Kowash, 2000)			the third year of the study. Group D: DHE as **diet and oral hygiene instruction once a year only** for each of the 3 years.	
Quinonez (2006), USA	To examine the cost-effectiveness of fluoride varnish application by medical providers when implemented within a well-child periodicity schedule for Medicaid-enrolled children.	CEA	9 mo at 1st model cycle to 42 mo at last cycle. No of participants is not stated.	Medicaid-enrolled children	Well-child visits (at medical centrel) during primary care. Modelling.	**Flouride varnish** at 9, 18, 24, and 36 mo (FV-all)	No intervention (FV-none)
Marino (2007), Chile	To assess the cost-effectiveness of a community denial caries prevention programme (using fluoridated powdered milk and milk-cereal), targeting preschool children living in non-fluoridated rural areas of Chile.	CEA	3 to 6 y.o. Total of 1,000 in the fluoridated milk/cereal group (repeated cross-sectional samples, which consisted of a fresh sample of individuals from each community taken at each of the examinations) and 1,000 in the control group (one of the study's assumptions). I.e. 250 for each age cohort: 3, 4, 5 and 6-y.o. in the	Children living in two communities matched based on geographic proximity, community size and similarity of caries prevalence. One community was the test (fluoridated milk/cereal, and the other the control (status quo).	Community	**Fluoridated milk and milk-cereal** (milk for 0-1-y.o; milk-cereal for 2-5-y.o.)	No intervention area (status quo), matched on geographical proximity, community size and similarity of caries prevalence.

Study first author (year of publication), country	Aim of study	Type of economic evaluation	Participants' age / Number of participants (within 2-5 y.o. range)	Participant description	Setting	Intervention(s)	Comparator(s)
			intervention/control group.				
Stearns (2012), USA	To estimate the cost-effectiveness of a medical office–based preventive oral health programme in North Carolina called Into the Mouths of Babes (IMB).	CEA	6 months at baseline (n=209,285).	Children enrolled in North Carolina Medicaid at 6 months of age and deemed to be continuously enrolled for at least an additional 12 months during 2000-2006. The children were followed up until they were 72 months of age or no longer enrolled in Medicaid.	Medical offices, dental offices or hospitals.	Into the Mouths of Babes (IMB) programme: physicians are reimbursed by Medicaid to conduct **dental screenings** of children under 3 y.o., apply **fluoride varnish**, and **counsel parents**. Children are referred to dentists, if needed.	Children with no IMB visits.
Pukallus (2013), Australia	To examine the costs and patient outcomes of a prevention programme for early childhood caries to assess its value for government services.	CEA	6 mo (modelled up to age 6 y). No in cohort not stated. There were 89 chn in the telephone prevention programme arm, 58 of them remained at the end of study. 40 chn in Usual Care group. **(Data from Plonka, 2013).**	Public dental patients in a low socioeconomic, socially disadvantaged area in the State of Queensland, Australia.	Public dental patients	**Telephone OH education programme** (at child ages 6mo, 12 mo and 18mo) and **toothbrushes + toothpaste posted** to home addresses. (With underlying water fluoridation.)	Usual care

Study first author (year of publication), country	Aim of study	Type of economic evaluation	Participants' age / Number of participants (within 2-5 y.o. range)	Participant description	Setting	Intervention(s)	Comparator(s)
Ataniyazova (2014), Uzbekistan	To apply CBA framework to investigate economic viability of hand hygiene and oral health interventions aimed at kindergarten age children (3-6 y.o.) on respiratory diseases (influenza, bronchitis, pneumonia), intestinal diseases (diarrhoea, hepatitis A, and helminthiasis), and dental caries and stomatitis.	CBA	Kindergarten age children (3-6 y.o.). Various hygiene interventions covered different numbers of children. Toothbrush and toothpaste distribution covered 964 children.	Kindergarten children (no further information provided).	Kindergartens in Tashkent city	Kindergarten-based hand hygiene and oral health promotion intervention (combined). **OH promotion** included: **toothpaste, toothbrushes, OH education** materials.	No intervention.
Chi (2014), USA	To compare the incremental cost-effectiveness of 2 primary molar sealant strategies—always seal and never seal—with standard care for Medicaid-enrolled children.	CEA	Enrolment files from Iowa Medicaid were used to identify children < 6 years. N/A, as it's a tooth-level model.	Enrolment files and dental claims from Iowa Medicaid (children < 6 years)	Dental practice	Two **primary molar sealant** strategies: 1) always seal; 2) never seal.	Standard care
Ney (2014), USA	To evaluate 2 primary molar sealant strategies (always seal (AS) and standard care (SC)) for publicly insured children using an “expected value of perfect information”	CEA and “expected value of perfect information” (EVPI) approach.	3 y.o. 1,250-observation child-level model (per correlation model: high and low intra-child correlation)	3 y.o. enrolled in Medicaid or the State Children’s Health Insurance Plan (SCHIP)	Modelling	2 **primary molar sealant** strategies: a) always seal; b) standard care.	See "Interventions" box

Study first author (year of publication), country	Aim of study	Type of economic evaluation	Participants' age / Number of participants (within 2-5 y.o. range)	Participant description	Setting	Intervention(s)	Comparator(s)
	(EVPI) approach.						
Koh (2015), Australia	To evaluate the cost-effectiveness of a home-visit intervention conducted by oral health therapists relative to a telephone-based alternative and no intervention.	CEA and CUA	Model starting age for children was 6 mo. 188 children in Home Visits group; 58 children in Telephone Contacts group; 40 in Usual Care group. **(Data from Plonka, 2013).**	Mothers presenting to public maternity health clinics were invited to participate in the study. The interventions were provided when the children were aged 6, 12, 18, 30 and 42 months and clinical assessments were performed at 24, 36, 48 and 60 months.	Multiple, also depending on the study arm: home, community dental clinic.	The home-visit intervention consisted of five 6-monthly **home visits** by oral health therapists, where they provided **dental examinations** of the children and **dental care instructions** to the mothers, for durations of approximately 30 minutes. The **telephone intervention** consisted of five 6-monthly telephone calls delivering **dental care instructions** by the oral health therapists. The telephone calls were between 15 and 20 minutes of duration, and instructions included **tooth brushing and dietary advice**. The home visits and telephone intervention groups were examined clinically at ages 24, 36, 48 and 60 months by dental practitioners blinded to group allocation.	The usual care groups were children aged 24 and 60 months who were the reference control children of the study and received dental examinations at the community dental clinic. The usual care group received no prior dental contact.
Samnaliev (2015), USA	To assess the cost-effectiveness of a pilot disease management (DM) programme aimed at preventing early childhood caries among children younger than 5 years.	CEA	Average 39 mo. DM group: Total N = 395; <3yo = 161 (41%); 3-<4y.o. = 148 (37%); 4-<5y.o.= 86 (22%). Baseline comparison group (historical control): Total N = 123; <3yo	DM group: < 5 y.o. at baseline; had active caries or history of caries; returned for at least two subsequent visits; had complete study data.	Dental clinic at a children's hospital	A **complex DM protocol**: 1) In-office management: assessing caries risk at each visit, applying **fluoride varnish** and setting **self-management goals (SMGs) for home care**. 2) Parents were given the full options for **restorative treatment.** 3) If destruction of the tooth structure by the caries	Historical control (baseline) data were obtained of patients younger than 60 months of age who initiated conventional dental treatment at the hospital between 2004 and 2006. A computer-generated randomized scheme was used to identify patients and subsequently reviewed their

Study first author (year of publication), country	Aim of study	Type of economic evaluation	Participants' age / Number of participants (within 2-5 y.o. range)	Participant description	Setting	Intervention(s)	Comparator(s)
			= 51 (41%); 3-<4y.o. = 44 (36%); 4-<5y.o.= 28 (23%).			process was minimal, **caries arrest** was possible with remineralization of the tooth structure. 4) When the decay had progressed into dentin and caries arrest was not achieved, **interim therapeutic restoration (ITR)** was offered. 5) For the at-home protocol, parents were presented with a menu of SMGs to work on before the next visit. Goals included basic caries control strategies: more frequent **tooth brushing, using topical fluorides at home,** and **modifying the diet.** 6) A **0.4 percent stannous fluoride** (1,000 ppm fluoride) was recommended to be applied judiciously two or three times per day by the parent. Or parents may elect to use over-the-counter 1,000 ppm fluoride toothpaste.	billing records.
Atkins (2016), USA	To conduct a cost-effectiveness analysis of five specific dental interventions to help guide resource allocation.	CEA	6-60 mo. "The number of children receiving each intervention varied". (See paper.) **[It seems to be complicated and not clearly defined**	Alaska Native children residing in the Yukon–Kuskokwim Delta region of Alaska	Dental clinic or hospital or residing in a fluoridated area - depending on the intervention	Five interventions were compared: 1) **water fluoridation**, 2) **dental sealants**, 3) **fluoride varnish** applications, 4) **home tooth brushing** with fluoride toothpaste, and 5) conducting initial **dental exams** on children less than 18 months of age with parents receiving **parental**	See "Interventions" box

Study first author (year of publication), country	Aim of study	Type of economic evaluation	Participants' age / Number of participants (within 2-5 y.o. range)	Participant description	Setting	Intervention(s)	Comparator(s)
			within the paper.]			**counselling**.	
O'Neill (2017), UK	To measure the effects and costs of a combined fluoride intervention designed to prevent caries in young children attending dental services.	CEA	Mean = Median = 3.1 y.; Range: 2-4 y. (n=1248)	Chn aged 2 to 3 y but not yet 4 y old, caries free (into dentine), and registered with the 22 NHS dental practices recruited into the trial. Children were excluded if they had a history of fillings or extractions due to caries, fissure sealants on primary molar teeth, and/or a history of severe allergic reactions requiring hospitalization.	NHS general dental practices (n=22)	Intervention included 3 components: 22,600 ppm of **fluoride varnish** applied to all primary teeth by the children's dentist; a **free toothbrush** and 50-mL tube of 1,450 ppm of **fluoride toothpaste**; standardized **dental health education** on optimal use of fluoride toothpaste and restriction of sugar consumption. The intervention was provided at the child's dental check-up, twice a year at approx. 6-mo intervals. Participants were followed up for 3 y.	Control group: received the same standardized dental health education as the intervention group, every 6 mo at their dental check-up.

References:

Kowash MB, Pinfield A, Smith J, Curzon MEJ. Effectiveness on oral health of a long-term health education programme for mothers with young children. British Dental Journal. 2000; 188: 201-05.

Plonka KA, Pukallus ML, Barnett A, Holcombe TF, Walsh LJ, Seow WK. A controlled, longitudinal study of home visits compared to telephone contacts to prevent early childhood caries. International journal of paediatric dentistry. 2013; 23: 23-31.

Appendix 8 Full EEs: Methods, results and authors' conclusions

Study first author (year of publication), country	**EE methods**	**Results** (outline, including sensitivity analysis)	**Authors' conclusions**
Donaldson (1986), UK	The costs of the preventive programme were compared with the costs of restoring the carious surfaces that would have been expected to occur without the prevention programme. Costs of the prevention programme included materials, such as fissure sealants, fluoride drops / tablets, pastes, gels and educational materials [not reported by an individual item]. The costs of the restorative care provided within the preventive programme were not included because they would have been the same irrespective of whether or not the children had participated in the programme or had simply presented for traditional restorative care. The number and costs of routine dental examinations, which included scaling and polishing, were assumed initially to be the same in both the preventive and restorative regimes. The costs of restoring the carious surfaces that would have been expected to occur without prevention were estimated by multiplying the annual reductions in dmfs and DMFS by the appropriate fee for an amalgam filling in a single surface cavity.	The incremental cost per reduction in dmfs in the preventive programme was £3.47 for the 4-6 age group (age at the end of study) and per reduction in DMFS in 7-10-year-olds was £9.44. When compared to the cost of restorative care (single surface amalgam) of £2.93, this resulted in a ratio of preventive and restorative costs of 1.18 and 3.22, respectively. Results of sensitivity analyses were also reported.	The cost-effectiveness analysis identified the issue of differences in the quality of output as critical to choices between the two treatment regimes. The preventive programme was primarily intended for preschool children; for this younger group, assumptions about the quality of the preventive outcome would have to value it at between 0.8 and 1.2 times the quality of the restorative outcome in order to make up the difference in cost between the two regimes. For 7–10 years olds, the 4-year analysis showed the preventive programme to be more costly than restorative care largely because of low rates of incremental change at these ages.
Widenheim (1991), Sweden	Based on interview data, 304 subjects (born 1967 in Lund, Sweden) were divided into five groups with different periods of NaF tablets consumption and one group with no intake. Records from the Public dental Service clinics were examined. Filled surfaces (fs, FS) were registered for each child: a) in all permanent	A statistically significant difference was found in fs at 8 yr ($P < 0.001$) and in FS at 17 yr ($P < 0.01$) between children who had taken the tablets regularly from the first year of life to age 5–7 yr (fs = 1.9; FS = 3.8) and the non-consumers (fs = 5.2; FS = 5.9). In the other four tablet groups, both the fs and the FS values tended to decrease with increasing duration of intake. The prevalence of approximal caries also tended to decrease, as regards both dfs and DFS, with	The results show that a regular intake of NaF tablets during preschool period had a cariostatic effect in both dentitions, related to starting age and to duration of intake. Most of the caries reduction was observed in the primary teeth. The measure was economically profitable when the tablets were taken daily throughout

Study first author (year of publication), country	**EE methods**	**Results** (outline, including sensitivity analysis)	**Authors' conclusions**
	teeth at 17 yr.; b) in primary molars and canines at 8 yr. of age. A maximum total of 24 approximal surfaces were examined for permanent teeth (DFSa) and a maximum of 20 approximal surfaces for primary teeth (dfsa). CEA was performed comparing the cost of the NaF tablet programme to restorations in permanent and primary teeth. The following NaF costs were included: average cost of labour of a dentist, dental hygienist or chairside assistant (25 min/child over 5 years, at 300 SEK/h), costs of NaF tablets (6 SEK per 100 tablets). Parental time off work, child time off school and travel costs were not included. Restoration of 1 tooth surface requited 20 min treatment, at a charge of 175 SEK (Swedish Dental Insurance system). Cost per surface saved and CER were calculated for various scenarios.	increasing duration of tablet consumption, with a statistically significant difference ($P < 0.001$) in primary teeth between children with the longest intake (dfs = 1.4) and non-consumers (dfs = 4.9). The cost-effectiveness ratio was approximately 1:1 for both dentitions. Most of the effect was obtained in the primary dentition. When comparing the longest regular NaF consumption group with the non-consumers group, in the baseline scenario (0% discount rate, costs of tablets included), the costs per surface saved were 163 SEK for permanent teeth, 105 SEK for primary teeth and 64 SEK for both dentitions combined. CERs were 1:1.0, with a mean loss of around 13 SEK per child; 1:1.5, with an average gain of 169 SEK per child; and 1:2.5, with a 501 SEK gain per child, respectively. When 10% discount rate was applied, the mean gain per child decreased from 501 SEK to 215 SEK (for both dentition combined). When the NaF tablets costs were excluded, the mean gain per child was 379 SEK, with CER 1:5.0.	preschool period. On the assumption that the parents paid for the tablets, this seems to be valid to a certain extent on a community basis in a population where only about 20% of children follow the recommended scheme.
Ramos-Gomez (1999), USA	The authors estimated the cost-effectiveness of prevention programmes for ECC in a hypothetical cohort of 1-year-old children followed over a five-year period, making assumptions about the costs and impacts of a proposed programme based on available evidence and, in some cases, clinical judgment. The estimated cost of each intervention was based on 1996-97 California Dental Medicaid reimbursement rates and rates for the Spokane Dental Prevention Project. Treatment costs were derived from a group of 115 patients with ECC treated at a paediatric dental clinic (University of California, San Francisco) in 1992. A number of authors' own assumptions was also used.	The following is reported by the type of intervention – Minimal, Intermediate and Comprehensive. Effectiveness: 40%, 70% and 80%; 5-year cumulative cost of prevention (per child): $314, $497, $570; No of carious surfaces averted (per child): 4.32, 7.32, 8.36; cost per carious surfaces averted (per child): $72.69, $65.74, $66.28. The intermediate intervention is the most cost-effective, as its cost per carious surface averted is the lowest ($65.74). Dividing the cost per carious surface averted ($65.74) by the cost of treatment per surface ($112) yields a cost saving threshold of 59%. I.e. prevention becomes cost-saving if at least 59 percent of carious lesions receive restorative treatment.	The proposed interventions would be cost saving if at least 59 percent of the carious surfaces would have been treated. Comprehensive intervention would provide the greatest oral health benefit; however, because more children would receive reparative care, overall programme costs would rise even as per-child treatment costs decline.

Study first author (year of publication), country	**EE methods**	**Results** (outline, including sensitivity analysis)	**Authors' conclusions**
Davies (2003), UK	Calculations of the costs of establishing and running the programme (if the programme was run by a typical salaried dental service on a population cohort in the UK): labour costs, overheads and product costs.	The total programme cost (of establishing and running) over 4.5 years was £149,265. Cost per dmft reduction (tooth saved) = £80.83. Cost per child kept free from caries experience = £424.38. Cost per child kept free from extraction experience = £679.01	The programme achieved a significant caries reduction in children who received 1450ppm fluoride toothpaste and the costs are now available to those considering provision of treatment services in areas where children are at high caries risk.
Kowash (2006), UK	Costs of the DHE programme were calculated. Leeds DHE Programme was assessed as a Preventive Programme in the Hypothetical Community of Niessen and Douglass (1984) and was compared with community water fluoridation (CWF) and school-based fissure sealant programmes (FSP) and also with the Leeds slow releasing fluoride glass devices (SRFD) programme from other studies / reported in other papers. Caries reduction (%), number of carious surfaces saved, costs, benefits, B/C and C/E ratios were calculated for each of the compared programmes. [The methods section is not clearly written and many details are missing.]	Total cost of the DHE programme was £12,891. The savings in costs of restoring the 'saved' carious surfaces was estimated at £36,386. B/C ratio was 5.6; C/E ratio was 1.8 (i.e. the cost to save one carious surface was £1.8 pounds). Results from the hypothetical cohort modelling: the cavities saved over the three year period indicated a B/C ratio for the DHE of 5.21 compared with SRFD of 4.17; CWF of 1.15 and FSP of 0.42. The C/E results were 1.92, 2.40, 8.66 and 23.74 respectively.	The DHE programme gave better benefit-costs and costs effectiveness ratios than other preventive programmes. The cost of such DHE study paradigm could be further minimised by having suitably trained midwives and health visitors giving the DHE messages to mothers during their routine home visits.
Quinonez (2006), USA	Cost-effectiveness was analysed using published probabilities and costs. Input parameters included the effectiveness of fluoride varnish (35.4%) applied according to the well-child periodicity schedule up to 3 years of age at $16.00 per application, annual caries increment (14%), age-specific dental care usage rates (0.2% at 9 months to 19% at 42 months), and age-related nonhospital treatment costs ($292.00-$503.00) and hospital treatment costs ($2191.00-$2940.00). Sensitivity analysis was conducted to assess the effects for varying input parameters.	FV improved clinical outcomes by 1.52 cavity-free months but at a cost of $7.18 for each cavity-free month gained per child and $203 for each treatment averted. Considerable uncertainty existed for some parameters. Fluoride varnish was cost saving when dental services and nonhospital treatment costs were 1.5 to 2 times greater, respectively, than our base case estimate.	Based on the assumptions, fluoride varnish use in the medical setting is effective in reducing early childhood caries in low-income populations but is not cost saving in the first 42 months of life. Potential total cost reductions with varying parameters suggest that evaluations using a longitudinal cohort are needed.

Study first author (year of publication), country	**EE methods**	**Results** (outline, including sensitivity analysis)	**Authors' conclusions**
Marino (2007), Chilie	The results of a community trial lo measure the effects of using fluoridated powdered milk and milk-cereal to prevent dental caries, together with the cost of running the programme, were used to determine its cost-effectiveness when compared to the status-quo alternative. In the experimental community, fluoridated milk products were given to approximately 1,000 children aged between six months and six years, using the standard National Complementary Feeding Programme available in Chile. The control group received the milk products only. Dental caries status was recorded at the beginning and end of the programme in both communities using WHO criteria. The costs that would be incurred by such a programme, using a societal perspective, were identified and measured.	Children who received fluoridated products had significantly lower mean levels of dental caries than those who had not. This improvement was achieved with a yearly cost of RCH$ 1,839.75 (1999, Chilean pesos) per child (1 US$ = RCH (1999) $527.70). A total value of 1999 RCH$ 7,358,292 was estimated for the four-year programme. Costs of dental treatment were about 70% higher in the control group (RCH$ 28,351,391 or RCH$ 7,087.85 per child per annum) compared with the intervention group (RCH$ 16,709,620 or RCH$ 4,177.40 per child per annum). On average, this programme resulted in a net societal savings of RCH (1999) $2,695.61 per diseased tooth averted after four years when compared to the control group. Sensitivity analysis resulted in ICER ranging from a net saving of RCH$ 5,006.26 to a net cost of RCH $ 3,822.57 per drnft avoided. The most favourable result was gained by using the lower boundary of the effectiveness of the milk-ftuoridation scheme assumption, that is, using the lower extreme in the test community and the upper boundary in the control community. The least favourable result was found using the lower extreme in the control community and the higher boundary in the test community.	While the analysis has inherent limitations as a result of its reliance on a range of assumptions, the findings suggest that there are important health and economic benefits to be gained from the use of fluoridated milk products in non-fluoridated rural communities in Chile.
Stearns (2012), USA	The CEA used the Medicaid programme perspective and a propensity score–matched sample with regression analysis to compare children with 4 or more vs 0 IMB visits (children who had 1 to 3 IMB visits were excluded to avoid underestimating the C-E). Medicaid reimbursement codes identified IMB visits and caries-related treatments, including restorations, extractions, stainless steel crowns, and nerve-related treatments (pulpotomies/ pulpectomies). The payments for IMB recipients consisted of IMB visits plus all other services related to dental care, whereas only the latter component applied for children not receiving IMB visits. 3 categories of dental service payments were measured: 1)	Into the Mouths of Babes is 32% likely to be cost-saving, with discounting of benefits and payments. On average, IMB visits cost $11 more than reduced dental treatment payments per person. The programme almost breaks even if future benefits from prevention are not discounted, and it would be cost-saving with certainty if IMB services could be provided at $34 instead of $55 per visit. Sensitivity analyses results: Without discounting, the likelihood that having 4 or more IMB visits is cost-saving increased to 47.9%, so the programme is close to break even. The estimated maximum payment per IMB visit that could achieve cost-saving with virtual certainty ranged from $30.93 (full sample with discounting) to $34.84 (propensity score–matched sample without discounting). The programme is cost-effective with 95% certainty if Medicaid is willing to pay $2,331 per hospital episode avoided.	Into the Mouths of Babes improves dental health for additional payments that can be weighed against unmeasured hospitalization costs. The benefits may be worth the extra Medicaid payments from a societal perspective that encompasses all the costs of dental caries. Identification of the most effective components of the IMB service package and the costs of those components could determine the most appropriate rate for the IMB services.

Study first author (year of publication), country	**EE methods**	**Results** (outline, including sensitivity analysis)	**Authors' conclusions**
	Payments for hospital episodes for dental caries related treatment (CRT), including emergency department visits with caries as a main diagnosis, physician services including anaesthesiology, operating room expenses, overnight stays, and dentist services; 2) Dentist office visit payments for CRT; and 3) Dentist office visit payments for preventive services without CRT, including visits for planning treatments. Using predicted estimates of the likelihood of dental service use and Medicaid payments, the estimates were averaged across all children in each age-month and then the experience was aggregated over 6 to 72 months of age to estimate cumulative costs and effects.		
Pukallus (2013), Australia	A mathematical model (Markov model) was used to assess caries incidence and public dental treatment costs for a cohort of children. Healthcare costs, treatment probabilities and caries incidence were modelled from 6 months to 6 years of age based on trial data from mothers and their children who received either a telephone prevention programme or usual care. Sensitivity analyses were used to assess the robustness of the findings to uncertainty in the model estimates. Costs for the telephone intervention programme included: staff time for the delivery of the telephone intervention (including unanswered telephone calls), telephone call costs, packing and posting oral care products, and other administrative costs for recording, filing and recall items. Healthcare costs for all children included restorations, extractions and	By age 6 years, the telephone intervention programme had prevented an estimated 43 carious teeth and saved £69 984 in healthcare costs per 100 children. The results were sensitive to the cost of general anaesthesia (cost-savings range £36 043–£97 298) and the incidence of caries in the prevention group (cost-savings range £59 496–£83 368) and usual care (cost-savings range £46 833–£93 328), but there were cost savings in all scenarios.	A telephone intervention that aims to prevent early childhood caries is likely to generate considerable and immediate patient benefits and cost savings to the public dental health service in disadvantaged communities.

Study first author (year of publication), country	**EE methods**	**Results** (outline, including sensitivity analysis)	**Authors' conclusions**
	crowns.		
Ataniyazova (2014), Uzbekistan	CBA was employed. Cost of illness approach. The benefits consist of: (i) income saved by parents due to risk reduction in the incidence of disease; (ii) reduction in medical costs due to avoided illness; and (iii) budget resources saved. The costs were the cost of the hygiene promotion programme activities in the pilot kindergartens in 2011.	Expenditure on hand hygiene and oral health accounted for 52% and 48% of the total project expenses, respectively. Toothbrushes accounted for 19% of the total programme costs, while toothpaste accounted for 10%. Benefits (of the combined hand hygiene and OH promotion programme) outweighed costs at each discount rate level considered (6%-24%): at 6% discount rate the benefit-cost ratio was 1.97, while at 24% discount rate it was 1.07.	Within a large range of assumptions and discount rates used, hand washing and tooth brushing interventions are economically efficient and socially desirable.
Chi (2014), USA	A deterministic Markov model assuming 10 000 primary molars to estimate lifetime costs per tooth under each sealant strategy (standard care, always seal and never seal), the number of restorations or extractions avoided for each strategy, and the relative cost per event avoided. ICERs were generated, which compared costs and outcomes for 2 given strategies. Excel 2013 (for Markov models and simulations), SensIt 1.45 (one-way sensitivity analyses) and Stata 12.0 (probabilistic sensitivity analysis) were used.	The total costs of standard care were $214 510, always seal cost $232 141 and never seal cost $186 010 (i.e. always seal costs 8.2% more than does standard care and never seal costs 13.3% less). The average lifetime cost per tooth was $21.45 for standard care, $18.61 for never seal, and $23.21 for always seal. Relative to standard care, always seal reduced to 340 from 2389 the number of restorations, and never seal increased the number of restorations to 2853. Compared with standard care, the ICER of always seal was $8.60 per restoration avoided and $80.53 per extraction avoided. The ICER standard care compared with never seal was $61.18 per restoration avoided and $610.40 per extraction avoided. Relative to never seal, the ICER of always seal was $18.32 per restoration avoided and $173.43 per extraction avoided. The probabilistic sensitivity analysis indicated that compared with standard care, always seal cost $8.12 per restoration avoided (95% CI = $4.10, $12.26; P < .001). Standard care cost $65.62 per restoration avoided compared with never seal (95% CI = $52.99, $78.26; P ≤ .001). Compared with never seal, always seal cost $18.34 per restoration avoided (95% CI = $14.35, $22.34; P ≤ .001). Compared with standard care, always seal cost $71.93 per extraction avoided (95% CI = $35.11, $108.75; P ≤ .001). Standard care cost $571.30 per extraction avoided compared with never seal (95% CI = $389.21, $753.40; P < .001). Compared with never seal, always seal cost $160.98 per extraction avoided (95% CI = $121.87, $200.10; P ≤ .001).	The simulation models demonstrate that sealing primary molars prevents restorations and extractions but is more costly than is not sealing primary molars in Medicaid-enrolled children. Compared with the current standard of care, always sealing primary molars is more cost-effective than is never sealing primary molars.

Study first author (year of publication), country	**EE methods**	**Results** (outline, including sensitivity analysis)	**Authors' conclusions**
Ney (2014), USA	A 10,000-observation tooth-level cost-effectiveness simulation model comparing 2 primary molar sealant strategies – always seal (AS) and standard care (SC) – with a 1,250-observation child-level model. Costs per child per restoration or extraction averted were estimated. Opportunity losses under the AS strategy were determined for children for whom SC was the optimal choice. EVPI was determined by multiplying mean opportunity losses by the projected incident population of publicly insured 3-year-olds in the US over 10 years with costs discounted at 2%. All analyses were conducted under assumptions of high and low intra-child correlations between at-risk teeth.	Compared with SC, the mean difference in cost per child of AS was $13.52 (95% CI: –$1.03, $28.08), and the mean number of restorations or extractions averted under the AS strategy was 1.81 per child (95% CI: 1.65, 1.96), corresponding to an ICER of $7.49 per restoration or extraction averted (95% CI: $2.85, 12.12) (Table 1). The AS strategy cost $43.68 over SC (95% CI: −$5.50, $92.86) per child per restoration or extraction averted under the high intrachild correlation assumption and $15.54 (95% CI $7.86, $23.20) under the low intrachild correlation. Under high intra-child correlation, mean opportunity losses were $80.28 (95% CI: $76.39, $84.17) per child, and AS was the optimal strategy in 31% of children. Under low correlation, mean opportunity losses were $14.61 (95% CI: $12.20, $17.68) and AS was the optimal strategy in 87% of children. The EVPI was calculated at $530,813,740 and $96,578,389 (for high and low intrachild correlation, respectively), for a projected total incident population of 8,059,712 children.	On average, always sealing primary molars is more effective than standard care, but widespread implementation of this preventive approach among publicly insured children would result in large opportunity losses. Additional research is needed to identify the subgroups of publicly insured children who would benefit the most from this effective and potentially cost-saving public health intervention.
Koh (2015), Australia	A Markov model was built to combine data on dental caries incidence, dental treatments, quality of life and costs for a cohort of children from age 6 months to 6 years. The probabilities of developing caries and subsequent treatments were derived primarily from the key intervention study. The outcome measures were costs, QALYs and No of carious teeth prevented. One-way and probabilistic sensitivity analyses were used to test the stability of the model.	For every group of 100 children, the model predicted that having the home-visit intervention would save $167,032 and telephone contacts $144,709 over 5.5 years relative to no intervention (usual care). The home visits and telephone intervention would prevent 113 and 100 carious teeth (per 100 children) relative to no intervention in a period of 5.5 years. Sensitivity analysis showed that a lower rate of caries reduced the intervention's cost-effectiveness primarily through reducing general anaesthesia costs. The home visits and telephone interventions resulted in 7 and 6 QALYs, respectively, gained over the usual care group for the 100 children over 5.5 years. Both interventions were 'dominant', as they saved costs and produced health benefits over usual care.	Both the home visits and telephone-based community interventions conducted by oral health therapists were highly cost-effective than no intervention in preventing early childhood caries.
Samnaliev (2015), USA	Incremental costs and effects (avoided restorative or surgical treatment visits in the dental clinic or in the operating room) were estimated separately from the health care system and societal perspectives, and for each evaluation period as well as for the	DM programme participation was associated with fewer hospital operating room (OR) and dental clinic visits to receive restorative or surgical treatment within 3, 6, and 12 months ($P < 0.001$). Overall, DM programme participation was associated with net savings that increased in magnitude over time and became significant in the 12-month evaluation for both the health care system ($752, $P = 0.003$)	The DM programme appears cost-saving and cost-effective and has the potential to reduce health care costs. It is recommended that the programme be implemented and evaluated on a wider scale.

Study first author (year of publication), country	**EE methods**	**Results** (outline, including sensitivity analysis)	**Authors' conclusions**
	subgroup of Medicaid beneficiaries. The base-case analyses relied on generalized linear models with a log (for costs) and Poisson (for effectiveness) link. To explore uncertainty related to the choice of model, the effects of each confounder (patient age, gender, race, ethnicity and access to care factors) were examined. Incremental costs and effects were estimated using a 1:1 propensity score matching of DM and baseline patients. Regression models were chosen for the main analyses. Statistical uncertainty was incorporated using nonparametric bootstrapping. 1,000 random sample replicates were drawn from the original data and estimated the ICER for each sample. SAS 9.3 was used.	and societal ($669, P = 0.009) perspectives. When conducted from a Medicaid perspective (n = 361), savings associated with DM programme participation amounted to $89 (P = 0.08), $123 (P = 0.10), and $173 (P = 0.07) and hospital visits to receive restorative/surgical treatment in the dental clinic or in the OR decreased by 0.47 (P < 0.001), 0.47 (P < 0.001), and 0.51 (P = 0.003) per patient over 3, 6, and 12 months, respectively. The joint probability of the DM programme being associated with both lower costs and fewer restorative or surgical treatment visits compared with baseline: when assessed from a health care system perspective, this probability was 64.5%, 86.5%, and 99.2% over 3, 6, and 12 months, respectively. This probability was slightly lower when the analyses were conducted from the societal perspective – 61.5%, 81.9%, and 98.6% over 3, 6, and 12 months (due to additional non-health costs associated with increased visits to the hospital among DM participants). The joint probability of the DM programme being associated with both lower cost and less restorative or surgical treatment over 3 and 6 months (93.4% and 93.0%) was greater from the Medicaid compared with societal or health care system perspectives, but not in the 12-month evaluation (96.3% for Medicaid)	
Atkins (2016), USA	Excel-based cost calculations, based on Medicaid data, data from local dental databases and existing publications (e.g. on interventions' effectiveness).	All interventions reduce the number of adverse health outcomes observed in the population; however use of fluoride toothpaste and toothbrush prevented the greatest number of caries at minimum and maximum effectiveness for the current coverage level with 1,433 and 1,910, respectively. Consequently, use of fluoride toothpaste and toothbrush also prevented the greatest number of FMDRs (159 and 211) at minimum and maximum effectiveness. At an ideal population coverage (100% of the relevant population), dental sealants prevented the greatest number of dental caries (3,522 and 3,870) and FMDRs (390 and 428) at minimum and maximum effectiveness. All interventions produced a cost savings using the CER. Water fluoridation had the greatest cost benefit of preventing dental caries ($1,335) at minimum effectiveness and dental sealants had the greatest cost benefit in preventing caries ($3,387) at maximum	All of the dental interventions evaluated were shown to produce cost savings. However, the level of that cost saving is dependent on the intervention chosen.

Study first author (year of publication), country	**EE methods**	**Results** (outline, including sensitivity analysis)	**Authors' conclusions**
		effectiveness over 10 years at the current coverage levels. In comparison, water fluoridation also had the greatest cost benefit in preventing caries in children receiving FMDRS ($8,149) at minimum effectiveness and maximum effectiveness ($6,053).	
O'Neill (2017), UK	The mean cumulative costs per child incurred over the 3-y period in each arm of the trial were compared and then related to the primary and secondary outcomes achieved over the same period. NHS costs were subdivided into those related to the intervention, those associated with other oral health care (checkups, pulpectomies, etc.), and those associated with care provided by other health service professionals. For the intervention group, direct intervention costs comprised toothpaste and toothbrushes, fluoride varnish, and the time involved in applying fluoride varnish, as well as a dental checkup during the course of which the varnish was applied. In the control group, the 6-monthly visit to the dentist was treated as a checkup for cost purposes. The analysis compared the total NHS costs in each of the 2 arms of the trial in accordance with the levels of effectiveness for each arm. In additional analyses, parental costs were added to those falling on the NHS. ICERs were calculated to provide an estimate of the mean cost per additional unit of outcome. The ICERs were estimated following a bootstrapping exercise in which sample data were used to construct a sampling distribution of mean costs, effects, incremental costs, and effects and ICERs. Net monetary benefits (NMBs) were also calculated. In the absence of a threshold willingness to pay for the	- A 5% difference in caries prevalence (primary outcome) between the groups in favour of the intervention was found, but not statistically significant. For secondary outcomes, differences in episodes of pain (P = 0.81) and number of teeth extracted were not significant (P = 0.95). dmfs showed a significant difference in favour of the intervention group. Among the full sample, the intervention group had on average 1.3 fewer carious surfaces than the control group. - Average total costs per person were £1027 for the intervention arm and £816 for the control ($p<0.05$). With respect to direct costs, total health care costs, and total costs, statistically significant between-group differences were evident. In each case, the intervention group had higher costs, which was largely related to the cost of the intervention. - ICERs: The only statistically significant results were obtained with respect to carious surfaces (mean difference in health service costs / mean difference in number of carious surfaces = -251 (95% CI -454; -80); mean difference in total costs / mean difference in number of carious surfaces = -249 (95% CI -457; -79). It costed on average £2,093 for every child prevented from converting to caries (if only health service costs were taken in account, without parental costs), ns. - NMBs: Positive NMB was found only with respect to carious surfaces. This suggests that if society were willing to pay £1,000 per carious surface avoided, the intervention would deliver NMB of £1,063 (95% CI £298; £1,855) per carious surface avoided when the intervention and other costs associated with its generation are taken into consideration. - CE plane (carious surfaces): Lied in the northwest quadrant of the diagram – higher cost, negative outcome (i.e. carious surfaces avoided). - CEACs: The likelihood of the intervention being deemed cost-	The costs of providing the preventive intervention outweighed savings in treatment over the 3-y follow-up period. This intervention delivered in general dental practice is unlikely to produce a cost-saving for the NHS. Even with this evidence-based intervention and high levels of adherence, over a third of children developed caries. This finding, allied to the high costs of providing prevention in practice, does not make a convincing argument for policy makers to invest in this technology. Other interventions, delivered in other settings, may produce greater improvements in population health for lower costs.

Study first author (year of publication), country	**EE methods**	**Results** (outline, including sensitivity analysis)	**Authors' conclusions**
	various measures of effect, a threshold of £1,000 was assumed for each. Cost-effectiveness acceptability curves were generated with respect to each outcome to examine uncertainty around the threshold.	effective is highest with respect to carious surfaces avoided. - Sensitivity analyses: Dentists consistently overestimated delivery time, and adjusting for this reduced the intervention costs but did not have a material effect on cost-effectiveness or on NMB. Similar results were obtained with respect to other sensitivity analyses based on using nurses or hygienists to apply fluoride and limiting the focus of the analyses solely to dental costs. The reduction in staff costs (and exclusion of other health care costs) improved the cost-effectiveness ratio and NMB calculation, but the intervention remained potentially cost-effective only with respect to reducing carious surfaces.	

Appendix 9 The CHEERS checklist appraisal results

Study reference		Ataniyazova, 2014	Atkins, 2016	Chi, 2014	Davies, 2003	Donaldson, 1986	Koh, 2015	Kowash, 2006	Marino, 2007	Ney, 2014	O'Neill, 2017	Pukallus, 2013	Quinonez, 2006	Ramos-Gomez, 1999	Samnaliev, 2015	Stearns, 2012	Widenheim, 1991
Section / Item	**Item No**	**Rating: 1 (yes) / 0 (no) / N/A**															
Title and abstract																	
Title	**1**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Abstract	**2**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Introduction																	
Background and objectives	**3**	0	1	1	1	0	1	1	1	1	1	1	1	1	1	1	0
Methods																	
Target population and subgroups	**4**	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1
Setting and location	**5**	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Study perspective	**6**	0	1	1	0	0	1	0	1	1	1	0	1	0	1	1	0
Comparators	**7**	0	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Time horizon	**8**	1	1	1	1	1	1	0	1	1	1	1	1	1	1	1	0
Discount rate	**9**	1	1	1	1	0	1	0	1	1	1	1	1	0	N/A	1	1
Choice of health outcomes	**10**	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1	1
Measurement of effectiveness	**11a**	1	N/A	N/A	1	1	1	1	1	N/A	1	1	N/A	N/A	1	1	1
	11b	N/A	1	1	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	1	1	N/A	N/A	N/A

Study reference		Ataniyazova, 2014	Atkins, 2016	Chi, 2014	Davies, 2003	Donaldson, 1986	Koh, 2015	Kowash, 2006	Marino, 2007	Ney, 2014	O'Neill, 2017	Pukallus, 2013	Quinonez, 2006	Ramos-Gomez, 1999	Samnaliev, 2015	Stearns, 2012	Widenheim, 1991
Section / Item	**Item No**	**Rating: 1 (yes) / 0 (no) / N/A**															
Measurement and valuation of preference based outcomes	**12**	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A
Estimating resources and costs	**13a**	1	N/A	N/A	1	0	N/A	0	1	N/A	1	N/A	N/A	N/A	1	1	0
	13b	N/A	1	1	N/A	N/A	1	N/A	N/A	1	N/A	1	1	1	N/A	N/A	N/A
Currency, price date, and conversion	**14**	1	1	1	0	0	1	0	1	1	1	1	1	0	1	1	1
Choice of model	**15**	N/A	N/A	1	N/A	N/A	1	N/A	N/A	1	N/A	1	1	N/A	N/A	N/A	N/A
Assumptions	**16**	N/A	N/A	1	N/A	N/A	1	N/A	N/A	1	N/A	1	1	N/A	N/A	N/A	N/A
Analytical methods	**17**	1	1	1	1	0	1	0	1	1	1	1	1	1	1	1	1
Results																	
Study parameters	**18**	0	1	1	0	0	1	0	1	1	1	1	1	0	1	1	0
Incremental costs and outcomes	**19**	0	1	1	0	1	1	0	1	1	1	1	1	0	1	1	1
Characterising uncertainty	**20a**	0	N/A	N/A	0	0	N/A	0	0	N/A	1	N/A	N/A	N/A	1	1	0
	20b	N/A	1	1	N/A	N/A	1	N/A	N/A	1	N/A	1	1	0	N/A	N/A	N/A
Characterising heterogeneity	**21**	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	N/A	1	N/A	1
Discussion																	

Study reference		Ataniyazova, 2014	Atkins, 2016	Chi, 2014	Davies, 2003	Donaldson, 1986	Koh, 2015	Kowash, 2006	Marino, 2007	Ney, 2014	O'Neill, 2017	Pukallus, 2013	Quinonez, 2006	Ramos-Gomez, 1999	Samnaliev, 2015	Stearns, 2012	Widenheim, 1991
Section / Item	**Item No**	**Rating: 1 (yes) / 0 (no) / N/A**															
Study findings, limitations, generalisability, and current knowledge	**22**	0	1	1	1	1	1	1	1	1	1	1	1	0	1	1	1
Overall score (per paper)		8	18	20	13	8	20	8	17	20	18	19	20	8	18	18	12
Maximum score (per paper)		18	18	20	18	16	20	18	18	20	18	20	20	18	18	18	19
Overall score (% of maximum)		44%	100%	100%	72%	50%	100%	44%	94%	100%	100%	95%	100%	44%	100%	100%	63%
Other																	
Source of funding	**23**	0	0	0	0	1	1	1	1	1	1	1	1	0	0	1	0
Conflicts of interest	**24**	0	0	0	0	0	0	0	0	1	1	1	0	0	0	0	0

Appendix 10 Experts contacted in relation to general health-related quality of life instruments

- Dr William Furlong (General Manager Health Utilities Inc.) – in relation to the Health Utilities Index (HUI) use in preschool population. By e-mail.
- Dr Saroj Saigal (McMaster University) - Health Status Classification System Preschool (HSCS-PS) questionnaire, based on the HUI. By e-mail.
- Mapi Research Trust (an online library that centralizes information on patient reported outcome questionnaires, the Trust also distributes and manages these questionnaires; https://mapi-trust.org/, https://eprovide.mapi-trust.org/) – in relation to the Paediatric Quality of Life Inventory Generic Core Scale (PedsQL) and PedsQL Oral Health scale for toddlers (two to four years). By e-mail.
- Dr Katherine Stevens (University of Sheffield), the author of the Child Health Utility 9 Dimensions (CHU9D): a) a general discussion of what kinds of GHQoL and "disease-specific" (OHQoL) instruments were best to be used in the PT@3 trial; b) then I followed up with regards to using CHU9D in a preschool population and amending wording accordingly. By e-mail and a video call.
- Dr Lyndie Foster Page (University of Otago) – using the Child Health Utility 9 Dimensions (CHU9D) in dental health research, although their dental study used this instrument in older children (six- to nine-year-old). By e-mail, followed by a meeting in person, at a later date.

Appendix 11 Experts contacted in relation to oral health-related quality of life instruments

- Mrs Amy Caldwell-Nichols (FiCTION Administrator) – in relation to the Michigan OHQoL Scale and other questionnaires used in the FiCTION (Filling Children's Teeth: Indicated or Not?) trial. By e-mail.
- Dr Bhavna Pahel (University of North Carolina) - the Early Child Oral Health Impact Scale (ECOHIS). By e-mail.
- Dr Noelle Huntington (Harvard Medical School) - preschoolers parental proxy Paediatric Oral Health-Related Quality of Life (POQL) questionnaire. By e-mail.
- Dr Sara Filstrup (a paediatric dentist at Cambridge Paediatric Dental Associates, USA; the author of the Michigan OHQoL Scale) – in relation to the Michigan OHQoL Scale. By e-mail.
- Prof Georgios Tsakos (University College London) – OHQoL instruments in general and the Scale of Oral Health Outcomes for 5-year-old children (SOHO-5) in particular, discussing changing the original reference period in SOHO-5. By e-mail and a phone call.
- Dr Jenny Abanto (University of São Paulo) – in relation to choosing between the SOHO-5 and ECOHIS. By e-mail.
- Prof Zoe Marshman (University of Sheffield) an OHQoL expert – in relation to the Caries Impacts and Experiences Questionnaire for Children (CARIES-QC) questionnaire and the use of other OHQoL and GHQoL instruments in child oral health research; consulting on which OHQoL measure was best to be used in the PT@3, in the end of the decision making process the choice was between the ECOHIS and the SOHO-5. By e-mail and a phone call.

Appendix 12 General health-related quality of life instruments used for children aged 3-5 years

Instrument (Country of origin)	Age of child (years)	Respondent	Format of administering	Recall period	No. of domains (Items)	Pros	Cons
PedsQL, Paediatric Quality of Life Inventory (USA) *Generic Core Scale*	a) 2-4; b) 5-7	a) Parent; b) Parent, child	a-b) Questionnaire	a-b) Past 1 month; Also there is "Acute version" of same q-res: *past 7 days*	a) 4 (21); b) 4 (23)	- Short (1 page), - Widely used	- A fee has to be paid to use; - Does not allow to calculate QALYs
CHU9D for under 5-y.o., Child Health Utility 9D (UK)	(3)-5	Parent	Questionnaire	Today	9 + Q to rate child's health	- 2.5 pages long; - Simple; - Developed in the UK (utilities elicited from the UK general adult population); - The author (Dr Katherine Stevens) is willing to support us if we were to use this questionnaire. - QALYs can be calculated.	- New instrument, derived from CHU9D for older children; - Has not yet been validated (3 pilot studies are under way); - The recall period is "today".
WCHMP, Warwick Child Health and Morbidity Profile (UK)	0-5	Parent	Interview	- in general; - in last year (depending on question)	10 (28)		- Has to be interviewer administered; - Some questions are open ended; - 3 pages long.
Kiddy-KINDL (Germany)	3-6	Parent (Also a child version for 4-6 y.o.)	Questionnaire	Past week	6 (24) Plus a section of 22 additional questions	Free to use (for academic researchers); 2.5 pages long.	- The language in the questionnaire does not seem to be very "English". - - Has it been used in studies in the UK? - No information on validity or reliability of Kiddy-KINDL has been reported.
ITQOL, Infant Toddler Quality of Life	0-5	Parent	Questionnaire	Some scales ask about the past **4 weeks**,	47-item short-form (ITQOL-		Determination of the **licensing fee** is based on the review of all parameters of the information

Instrument (Country of origin)	Age of child (years)	Respondent	Format of administering	Recall period	No. of domains (Items)	Pros	Cons
Questionnaire (USA)				the global health items asks about health **"in general"** and the global change items asks as compared to **one year ago**	SF47); 97-item full-length version (ITQOL).		provided during the registration process. http://www.healthactchq.com/contact-us.php) YA was not able to source a sample questionnaire, but some of the wording seems to be too infant-oriented (e.g. nursing, rolling over, discomfort due to gas / teething). - Due to intellectual property considerations, **surveys are not made available for review prior to completion of a License Agreement.**
TAPQOL, TNO-AZL Questionnaire for Preschool Children's Health-Related Quality of Life (The Netherlands)	0.5-5	Parent	Questionnaire	Last 3 months	8 (43)		- Was constructed for children with chronic diseases; - Long – 9 pages; - Complicated structure of answers; - Has not been validated in the UK or other English-speaking countries.
HSCS-PS, Health Status Classification System Preschool (Canada)	2.5-5	Parent	Questionnaire	Usually (usual health, usual ability) However, in one study a recall period of 1 week was used.	10 domains; plus 2 additional Qs (not part of original HUI)	- Based on HUI systems; - Free to use (YA has acquired permission from authors); - Might be able to calculate QALYs in future – late 2016.	- No time frames in the questions (“usually”); - Long, 6 pages; - At present not possible to calculate QALYs, as utilities have not yet been developed for this preschoolers’ q-re.
TedQL.2 (UK)	3-8	Child	Interview	Usually	5 (23)		Child self-report. Requires an interviewer to administer.
FS II(R), Functional Status II(R)	0-16	Parent	Interview	? (No information found)	8 (43 or 13)		Interview administered to parent. Time to complete: Long: 15-30 min; Short: < 10 minutes

Instrument (Country of origin)	Age of child (years)	Respondent	Format of administering	Recall period	No. of domains (Items)	Pros	Cons
							YA wasn't able to get a q-re sample
Child Health Status Questionnaire (USA)	a) 0-4; b) 5-13	Parent	Questionnaire	Past month / past 3 months (diff. Qs)	a) 3 (16) b) 5 (35)		Only one paper published in 1979. (And one report by the same authors, same year). Hasn't been used since (?)
QWB, Quality of Well-Being Scale (USA)	4-18	Parent	Interview	Past 6 days	3 (3 + 27 symptoms)	Preference based measure, allows to calculate QALYs	- Interviewer administered; - Fee has to be paid; - Lower child age limit is indicated as 4 years old, whereas the children in the PT@3 study are from 3 years old.

Notes: QALY – quality adjusted life year; YA – Yulia Anopa (the thesis author).

Appendix 13 Oral health-related quality of life instruments used in children aged 3-5 years

Instrument (Country of origin)	Age of child (years)	Respondent	Format of administering	Recall period	No. of Items	Pros	Cons
ECOHIS – Early Child Oral Health Impact Scale (USA)	2-5	Parent	Questionnaire	*"child's entire life from birth until now"* A study by Li et al (2008) used *"previous 2 weeks"* (Li et al. 2008a, Li et al. 2008b)	13 (divided into 6 domains) Derived from Child Oral Health Quality of Life Questionnaire (COHQoL), which is aimed at older children / their parents (6 y.o. and over). 13 items taken from COHQoL's Parental Perceptions Questionnaire (PPQ) and Family Impact Scale (FIS).	- Was developed especially for preschool children (parental proxy); - Was used in a number of studies (especially of GA extractions).	Study by Li et al (2008) included 0-5y.o. children with a "dental problem" who underwent a "dental treatment". Two rounds of ECOHIS were administered – pre-treatment and 2 weeks after the dental treatment. → **Limited ability** to respond to change was demonstrated. The large majority of parents reported <u>low levels</u> of impacts in chn <u>pre-treatment</u>. (OH impacts in young chn are generally uncommon and not severe). The vast majority of the sample had carious lesions requiring a restoration - this problem commonly has no or very low levels of impact.
POQL – Paediatric Oral Health-Related Quality of Life (USA)	a) 2-7; b) 8-14; c) teen (>14)	**a) Parent**; b-c) Parent and Child self-report	Questionnaire	Past 3 months	**a)** 6 + 7 "FIS" + Qs on parental dental health / dental visits; b) 10 + c) 17 +	**a)** -Was developed especially for parents of young children (2-7y.o.); - Short; - Other sections of q-re capture family impact, parent's own dental health. Was found to be *"valid and reliable measure…for use in preschool… children", "the items on the preschool version, adjusted for*	*No large studies conducted using POQL: "..large scale studies of the general population and its specific subgroups are important next steps in testing the POQL"* (Huntington et al. 2011)

Instrument (Country of origin)	Age of child (years)	Respondent	Format of administering	Recall period	No. of Items	Pros	Cons
						developmental differences, showed strong sensitivity to change". *"POQL has high utility for use in both clinical assessments and large-scale population studies"* (Huntington et al. 2011) *"..good internal consistency"* (Braun et al. 2013)	
Michigan OHQoL Scale – Child Version; Michigan OHQoL Scale – Parent/Guardian Version. (USA) (Filstrup et al. 2003)	From 4 y.o (?)	a) Child; b) Parent GT, pers.comm.: **Parent**/ Guardian Version; 10 questions and can be used from 4 years old onwards (a shortened version was used with as young as 3 years of age).	Questionnaire	Not very clear: *"How much do you disagree/agree with the following?* *- My child has… / teeth are… "* Currently (?)	a) 9 b) 10	*"Michigan OHQoL Scale was designed in a clinic setting and remains it's only application (in contrast ECOHIS is intended for use in epidemiological surveys)",* (Pahel et al. 2007) FiCTION trial (Dundee/Newcastle) are using **child** self-complete version of MOHQoL.	YA found literature on several versions with different numbers of Qs. Which one is the final version?
SOHO-5 – the Scale of Oral Health Outcomes for 5-year-old children (UK)	Under 5y.o.	a) Parent; b) Child	a) Questionnaire b) Interview	Original – "ever"; GT suggested to use "12 months" for PT@3.	7	- Developed especially for children under-5 y.o.; - Short; - COH team collaboration in its development & validation;	Is still being used in several "pilot" studies; has been validated to some extent (as of summer 2014)

Instrument (Country of origin)	Age of child (years)	Respondent	Format of administering	Recall period	No. of Items	Pros	Cons
						- GT is supportive, ready to collaborate.	
Caries Impacts and Experiences Questionnaire for Children (CARIES-QC) (UK)	From 5-6 y.o. (?)	Child	Questionnaire	Generally / Now (?)	17	Zoe Marshman (author): "W*e are currently developing a child-centred caries-specific measure of OHQoL here in Sheffield which we plan to turn into a utility measure. The OHQoL measure should be finished and tested early 2015 with the final stage to turn it into a utility measure planned for 2016".*	- Self-report q-re (aimed for older children); - Is being currently developed, has not been validated
PedsQL – Oral Health scale (USA)	a) 2-4; b) 5-7; c) 8-12 d) 13-18	a) Parent; b-d) Parent, child	a-d) Questionnaire	Past 1 month	5	Short. Will work well as an add-on to the PedsQL Core Scale (if it was to be used).	

Notes: GT – Georgios Tsakos, YA – Yulia Anopa, COH – Community Oral Health section at the Dental School, University of Glasgow.

References:

Braun, P. A., K. E. Lind, T. Batliner, A. G. Brega, W. G. Henderson, K. Nadeau, A. Wilson and J. Albino (2013). "Caregiver Reported Oral Health-Related Quality of Life in Young American Indian Children." J Immigr Minor Health.

Filstrup, S. L., D. Briskie, M. da Fonseca, L. Lawrence, A. Wandera and M. R. Inglehart (2003). "Early childhood caries and quality of life: child and parent perspectives." Pediatr Dent 25(5): 431-440.

Huntington, N. L., D. Spetter, J. A. Jones, S. E. Rich, R. I. Garcia and A. Spiro Iii (2011). "Development and validation of a measure of pediatric oral health-related quality of life: the POQL." Journal of Public Health Dentistry 71(3): 185-193.

Li, S., S. Malkinson, J. Veronneau and P. J. Allison (2008a). "Testing responsiveness to change for the early childhood oral health impact scale (ECOHIS)." Community Dentistry and Oral Epidemiology 36(6): 542-548.

Li, S., J. Veronneau and P. Allison (2008b). "Validation of a French language version of the Early Childhood Oral Health Impact Scale (ECOHIS)." Health and Quality of Life Outcomes 6(1): 9.

Pahel, B., R. G. Rozier and G. Slade (2007). "Parental perceptions of children's oral health: The Early Childhood Oral Health Impact Scale (ECOHIS)." Health and Quality of Life Outcomes 5(1): 6.

Appendix 14 Comparison of the four shortlisted parental proxy OHQoL instruments

Instrument (Country where developed)	Age of child	Sensitivity / Responsiveness to change	Studies where the instrument was used?	Findings of studies / issues
SOHO-5 (UK) (Tsakos et al. 2012)	Under 5y.o., 5-6 y.o.	Before/after a dental "treatment" (not mentioned which exactly) (Abanto et al. 2013a) – showed moderate longitudinal construct validity… good internal and external (anchor based) responsiveness. …Is responsive to change and can be used in clinical trials.	1) UK: 269 child-parent pairs, 5 y.o. (Tsakos 2010) 2) Brazil: 193 child-parent pairs, 5-6 y.o; of those 154 pairs completed q-re post-treatment; children with/without caries and/or dental trauma (Abanto et al. 2013a). 3) Brazil: 193 child-parent pairs, 5-6 y.o. (with 159 test-retest sample) (Abanto et al. 2013b)(Abanto et al. 2013b)(Abanto et al. 2013b)(Abanto et al. 2013b) (Abanto et al. 2013b) 4) Brazil: 298 child-mother pairs, 5-6 y.o. (Abanto et al. 2013c) (Abanto et al. 2013a)(Abanto et al. 2013c)(Abanto et al. 2013c)(Abanto et al. 2013c) 5) Brazil: 335 child-parent pairs, 5-6 y.o.; children with/without caries and/or traumatic dental injuries (TDI) (Abanto et al. 2014b)	1) UK version, 5 y.o., UCL/Glasgow study: internal consistency reliability – the results were excellent throughout… The results in relation to construct validity indicated an excellent performance of the new measure. …presence of clinically diagnosed active dental caries was significantly associated with worse OHQoL (Tsakos 2010) [unpublished internal report] However, "parents tended to underrate their children's oral impacts, as parental perceptions of their children's OHQoL were lower than their children's self-reports." – unlike in the Brazilian study below. 2) Brazil: Parental version showed moderate longitudinal construct validity. …showed good internal and external (anchor based) responsiveness. Conclusion: is responsive to change and can be used in clinical trials. Both Ch. and P. versions presented satisfactory results, however the child self-report version performed better (Abanto et al. 2013a). 3) The Brazilian version demonstrated construct and discriminant validity, test-retest reliability and reproducibility properties… The SOHO-5 was able to clearly discriminate between children with and without a history of dental caries (mean scores 5.8 and 1.1, $p<0.001$ – parental q-re) …Excellent test-retest reliability (Abanto et al. 2013b) 4) Brazil: Findings indicate very good agreement for mother-child pairs, with mothers reporting equivalent OHQoL for their children as the children themselves. Thus, in case the children are unable to complete the SOHO-5, the mothers may be used as good proxies (Abanto et al. 2013c). 5) Brazil: In both (Ch. and P.) versions, caries was associated with worse children's OHQoL, for the total score and all SOHO-5 items ($P < 0.001$). In contrast, TDI did not have a negative impact on children's OHQoL. Families with higher income report better OHQoL at this age, independent of the presence of oral diseases (Abanto et al. 2014b).
ECOHIS – Early Child Oral Health Impact Scale (USA) (Pahel et	2-5	Large majority of parents reported low levels of impacts pre-treatment, despite that they reported that their child had a dental problem	1) 295 parents of 5.y.o.chn.; 6 parents for test-retest (Pahel et al. 2007). 2) Convenience sample of 101	1) English version (USA): ECOHIS scores indicating worse QoL were significantly associated with fair or poor parental ratings of their child's general & oral health (Pahel et al. 2007). 2) English version (Canada): Large majority of parents reported low levels of

Instrument (Country where developed)	Age of child	Sensitivity / Responsiveness to change	Studies where the instrument was used?	Findings of studies / issues
al. 2007)		requiring treatment. In this sample with low level of problems.. [it] has demonstrated some limited ability to respond to change. …Beyond these results, the sensitivity was fairly good (good sensitivity but a relatively high rate of false positive findings)… Although [it] has demonstrated some ability to be responsive to change on a group level, at an individual level, the instrument is rather imprecise…does not appear to be sufficiently precise to be used in a clinic setting (Li et al. 2008a) No statistically significant difference in mean B-ECOHIS scores over the 1-year period for all domains combined was observed (P = 0.40). However, a statistically significant difference in mean B-ECOHIS scores over the 1-year period was found for the domains 'child symptoms' (P = 0.03) and 'child psychology' (P = 0.02). The magnitude of the mean difference in mean B-ECOHIS scores was −0.24 (child symptoms) and −0.21	(94 with 2 sets of q-res) parents of 0-5y.o. chn.; pre dental treatment (restoration, pulpotomy, extraction, other) and 2 weeks after the treatment (ref.time was "previous 2 weeks") (Li et al. 2008a) 3) 104 chn undergoing GA, 2-7 y.o., mean age 4.1 years (4 arm RCT: 16+30+30+28; Controls filled out ECOHIS while child was on waiting list for GA. In these cases GA was carried out after the study) (Klaassen et al. 2009) 4) Conv.sample of 50 child-parent pairs (31 before & after; 19 after only); chn undergoing GA (Klaassen et al. 2008) 5) 260 child-parent pairs, 2-5 y.o. chn with ECC, traumatic dental injuries and malocclusion (Abanto et al. 2011) 6) 826 6-7y.o. schoolchildren (cross-sectional) in deprived area; 587 parents returned q-re (Leal et al. 2012) 7) 302 chn 6-7 y.o. with cavitated primary molars. Three treatment groups. 277 parental q-res at baseline & 160 one year later (before/after treatments) (Leal et al. 2013) 8) Cross-sectional, 1,296 preschoolers/parents, 3-5 y.o.;	impacts pre-treatment, despite that they reported that their child had a dental problem requiring treatment. In this sample with low level of problems.. [it] has demonstrated some limited ability to respond to change. …Beyond these results, the sensitivity was fairly good (good sensitivity but a relatively high rate of false positive findings)… Although [it] has demonstrated some ability to be responsive to change on a group level, at an individual level, the instrument is rather imprecise…does not appear to be sufficiently precise to be used in a clinic setting. 3) Denmark (Dutch version): Relatively low mean scores were found with relatively large SD for all groups, before and after treatment. Dental treatment under GA does improve children's OHQoL (positive changes in children's OHQoL are elicited by dental rehabilitation under GA) (Klaassen et al. 2009) 4) Denmark: Improved QoL score after treatment under GA. Treatment of the early childhood caries (ECC) causes some increase of the QoL score, but its severity is not necessarily indicating the outcome of this score. ECOHIS showed a positive change in children's OHQoL (Klaassen et al. 2008) 5) Brazil: The severity of ECC showed a negative impact on OHQoL ($p<0.001$) – in each domain and the overall score; whereas trauma and malocclusion did not (Abanto et al. 2011) 6) Brazil: The presence of untreated cavitated dentine lesions was the one that impacted least on the children's quality of life. Children that had had a tooth extraction due to caries, those presenting pulp exposure, fistula and abscess, and those that reported toothache at the moment of the oral examination had increased chances of also having higher B-ECOHIS scores, showing that both child and family quality of life were affected by the child's oral health condition (Leal et al. 2012) 7) Brazil: No statistically significant difference in mean B-ECOHIS scores over the 1-year period for all domains combined was observed (P = 0.40). However, a statistically significant difference in mean B-ECOHIS scores over the 1-year period was found for the domains 'child symptoms' (P = 0.03) and 'child psychology' (P = 0.02). The magnitude of the mean difference in mean B-ECOHIS scores was −0.24 (child symptoms) and −0.21 (child psychology). These domains reflected children's experience of pain, difficulty in sleeping and frustration/irritation because of oral problems (Leal et al. 2013) 8) Chinese (Hong Kong): Overall dental caries experience and particularly the presence of untreated decayed teeth were associated with ECOHIS overall and

Instrument (Country where developed)	Age of child	Sensitivity / Responsiveness to change	Studies where the instrument was used?	Findings of studies / issues
		(child psychology). These domains reflected children's experience of pain, difficulty in sleeping and frustration/irritation because of oral problems (Leal et al. 2013) …the ECOHIS scores changed as expected with the gradient of parent's perceptions of treatment outcome, providing evidence of the measure's responsiveness. …Chinese version of the ECOHIS was sensitive to dental treatment for children aged 5 years or younger with ECC under GA. The measure also appeared to be responsive to the dental treatment for dental caries with respect to caregivers' global transition judgement with the outcome (Lee et al. 2011).	20% had severe ECC and 15% had ECC (Wong et al. 2011). 9) 111 chn, under 5 y.o., mean age 4.1 years. Two groups: with severe ECC, mean dmft = 7.44 (waiting for GA treatment) and caries-free. Reference period was "1 month" (Lee et al. 2010) [used PedsQL as well] 10) 398 parents of 12-mnth old chn (comm.-based intervention study); 94 parents of 0-5y.o. (hospital dental clinic). In 101 sub-sample of comm.group – second round of ECOHIS 2 weeks after the first (Li et al. 2008b). 11) 47 children 2-5y.o.and parents. Within a period of four-weeks, 20% of the participants repeated ECOHIS (Martins-Júnior et al. 2012). 12) 81 child-parent pairs, 0-5 y.o. with severe ECC, before/after GA. 3 rounds: pre-GA, 1 month post, and 3 months post (Pakdaman et al. 2014). 13) Consecutive sample of 32 (only!) child-parent pairs; 0-5 y.o. with ECC (mean age 4.5yr), undergoing GA. Before/after: 1 day before GA and 3 months after (Lee et al. 2011).	domain scores. The severity of dental caries experience was associated with child and family impact as those with severe ECC were among those with the highest ECOHIS scores. Higher ECOHIS scores were found in parents with lower education or income level, or with children who were born in mainland China ($p < 0.05$), or with children who had decayed, missing, or filled teeth ($p < 0.001$). In multiple regression analyses, decayed teeth and filled teeth in primary dentition were the better predictors ($p < 0.001$) of the ECOHIS score among the various parent and child characteristics collected in this survey (Wong et al. 2011). 9) Chinese (Hong Kong): ECOHIS shows better discriminant property between children with S-ECC and caries-free children than the generic measure, PedsQL™ 4.0. The ECOHIS appears more sensitive than PedsQL™ 4.0 in assessing the impact of dental caries on the life quality of preschool children. The mean total ECOHIS score of the caries-free group was significantly lower than those of the S-ECC group ($P < 0.001$). Furthermore, the child impact score was significantly lower among caries-free group compared to those of the S-ECC group ($P = 0.001$), and the family impact score was also significantly lower among caries-free group compared to those of the S-ECC group ($P < 0.001$). For the PedsQL™4.0, besides the subscale of physical functioning, which shows a significant difference between the two clinical groups ($P = 0.04$), no statistical differences was found between the S-ECC group and caries-free group for PedsQL™4.0 scores ($P = 0.23–0.68$). The ECOHIS score and subscale scores correlated strongly with the dmft and dmfs indices ($r > 0.595$; $P \leq 0.01$). There was a high correlation between the number of decayed teeth (dt) ($r = 0.662$), decayed surfaces (ds) ($r = 0.686$) and ECOHIS scores ($P \leq 0.01$). A moderate correlation was also found with filled teeth (ft) ($r = 0.243$; $P < 0.05$) and filled surfaces (fs) ($r = 0.256$; $P \leq 0.01$). The correlation of ECOHIS scores with missing teeth (mt/ms) was weak ($r = 0.156$) and was not statistically significant. No significant correlation was found between the PedsQL™4.0 scores and the caries status (Lee et al. 2010) 10) French language (Canada): The results… indicated that Cronbach's alpha was 0.79 for each of the child and family impact sections and 0.82 for the whole scale, the intra-class correlation coefficient was 0.95, total ECOHIS scores correlated with a global evaluation of oral health and the French ECOHIS was able to discriminate between children in the community with no expressed need for dental care and those in a dental clinic with an expressed need for dental care. French language version of ECOHIS has good internal consistency test-retest reliability, convergent validity and discriminant validity. It is therefore appropriate to use it to describe OHQoL in 0–5 year olds with French-speaking parents in Quebec and potentially in

Instrument (Country where developed)	Age of child	Sensitivity / Responsiveness to change	Studies where the instrument was used?	Findings of studies / issues
			14) 138 chn, 5 y.o., internal migrants (China) / parents; mean dmft = 5.17; 52% with rampant caries – caries in >=2 smooth surfaces of maxillary incisors (Gao et al. 2011) 15) Cross-sectional, 1,215 child-parent pairs, 1-4 y.o.; looked at traumatic dental injuries, malocclusion and caries; 80% had not experienced dental caries (dmft=0); mean dmft = 0.72 (Abanto et al. 2014a) The Chinese, Farsi, Spanish and Lithuanian language versions have been also validated. [YA stopped reviewing studies that used ECOHIS at a point when a decision was made not to use this questionnaire in the PT@3 study. More publications exist, which were not reviewed.]	other French-speaking populations in the world (Li et al. 2008b). 11) Brazilian version: …good construct validity, discriminant validity and internal consistency as well as acceptable test-retest reliability. The Brazilian Portuguese version of the ECOHIS is therefore a valid instrument for assessing oral health-related quality of life in preschool children with Brazilian Portuguese-speaking primary caregivers. It would be useful to evaluate the sensitivity and responsiveness of this measure using a longitudinal study in order to assess the effectiveness of oral healthcare interventions (Martins-Júnior et al. 2012). 12) Iran (Farsi version): …significant improvement was observed in both child and parent sections after dental rehabilitation (Pakdaman et al. 2014). 13) Chinese (Hong Kong): Among the sample whose caregivers perceived their child's condition was 'better' after treatment, there was a significant change in the total ECOHIS scores (P = 0.002). There were also significant changes in the CIS scores (P = 0.005) and three of the four sub-domains: child symptoms (P < 0.001), child function (P = 0.005) and child psychology (P = 0.013), and in the FIS scores (P = 0.002) and among the sub-domain of parental distress (P = 0.001). Among the sample whose caregivers perceived 'no change' in their child's condition, there was no significant difference in the total ECOHIS scores (P > 0.05), in the CIS scores or any of the sub-domains (P > 0.05) and in the FIS scores or any of the sub-domains (P > 0.05)… among the sample whose caregivers perceived that their child's condition was 'better' after treatment, there was a significant change in ECOHIS scores and the magnitude of such change was moderate to large. However, for those who did not perceive a benefit in their child's condition, their ECOHIS scores did not change significantly with treatment. The mean change in the total ECOHIS scores among caregivers who reported an improvement in their child's condition after treatment was almost seven times that of those who reported no change. At the domain level, the mean change of scores was double. A clear gradient in the expected direction across the categories of the global transition judgement was shown. Thus, the ECOHIS scores changed as expected with the gradient of parent's perceptions of treatment outcome, providing evidence of the measure's responsiveness. …Chinese version of the ECOHIS was sensitive to dental treatment for children aged 5 years or younger with ECC under GA. The measure also appeared to be responsive to the dental treatment for dental caries with respect to caregivers' global transition judgement with the outcome (Lee et al. 2011). 14) Chinese: The impacts of children's oral health on their QoL were considerable,

Instrument (Country where developed)	Age of child	Sensitivity / Responsiveness to change	Studies where the instrument was used?	Findings of studies / issues
				with 60.2% reported one or more impacts. The mean (SD) of the total ECOHIS score was 10.33 (8.91), with a median (inter-quartile range) as 11.0 (18.0). The oral health impact was high in the sub-domains of 'child symptoms' (51.5% with one or more impacts) and 'child function' (46.2% with one or more impacts), substantial on 'child psychology' (32.6% with one or more impacts) and 'parental distress' (37.2% with one or more impacts), and low on 'self-image and social interaction' (11.6% with one or more impacts) and 'family function' (17.1% with one or more impacts)… Findings from our study have identified dental caries experience and place of birth as key predictors of oral health-related QoL (Gao et al. 2011). 15) Brazilian: The presence of complicated traumatic dental injuries and dental caries were associated with worse OHQoL of Brazilian preschool children, whereas malocclusions do not… The presence of dental caries showed to have a negative impact for all the domains included in the children and family impact sections ($P < 0.05$) and for total B-ECOHIS scores (PR = 3.09; $P < 0.001$).
POQL – Paediatric Oral Health-Related Quality of Life (USA) (Huntington et al. 2011)	2-7	At the 6-month recall ECC chn were rated by their parents as having significantly improved oral health and physical, mental, and social functioning comparing to the baseline. By contrast, improvements in emotional functioning were not seen… QoL was relatively constant for the ECC group between 6 and 12-m follow-up visits. Surgical dental intervention resulted in significant improvement on OHQoL in the first 6 months and remained improved after 12 months… The positive effects of a dental intervention for ECC chn are significant at the 6- and 12-months follow-ups, and enhance QoL in multiple	1) Diverse child populations in both school-based and clinic-based settings; data collected btw 2005-2008; 1,140 parental q-res analysed (Huntington et al. 2011) 2) 501 parents of 2-8 y.o. chn (315 caries-free & 186 with ECC); at baseline (before) and at 6 and 12 months after "dental treatment for ECC" (they also say "surgical dental intervention") (Cunnion et al. 2010) 3) 143 caregivers of young American Indian chn, mean age 2.1 years (range 0 – 7.25 y.o.); cross-sectional (Braun et al. 2013) No clinical dental	1) POQL is a valid and reliable measure of OHQL for use in preschool, school-age, and preteen children. Equivalent parent report and child versions were validated for older children and preteens, and the items on the preschool version, adjusted for developmental differences, showed strong sensitivity to change. With only 10 items, the POQL has high utility for use in both clinical assessments and large-scale population studies. The development of the items on the POQL, and tests of its psychometric properties, involved oversampling from low-income and minority communities so that the voices and opinions of traditionally underserved populations were not overshadowed by the majority population… Scores for children with caries were about 50% greater than scores for children without caries (Huntington et al. 2011). From YA e-mail correspondence with N. Huntington, the author: "The Preschool version showed great sensitivity to change in our study of kids undergoing surgical treatment for severe ECC." 2) At the 6-month recall ECC chn were rated by their parents as having significantly improved oral health and physical, mental, and social functioning comparing to the baseline. By contrast, improvements in emotional functioning were not seen… QoL was relatively constant for the ECC group between 6 and 12-m follow-up visits. Surgical dental intervention resulted in significant improvement on OHQoL in the first 6 months and remained improved after 12 months… The positive effects of a dental intervention for ECC chn are significant at the 6- and 12-months follow-ups, and enhance QoL in multiple domains …This study also supports the validity of

Instrument (Country where developed)	Age of child	Sensitivity / Responsiveness to change	Studies where the instrument was used?	Findings of studies / issues
		domains …This study also supports the validity of items included into the parental version of the preschool POQL (Cunnion et al. 2010).	assessment data for this study.	items included into the parental version of the preschool POQL. 3) The impact scores of the POQL scale had good internal consistency, with a standardized Cronbach alpha coefficient of 0.78. The majority of caregivers reported favourable POQL for their children. The mean POQL score was 4.2 (on a scale from 0 to 100, where a higher score indicates worse POQL). Only a minority of caregivers reported their children had experienced pain, anger, crying, worrying, difficulty with eating, or missed school/daycare related to their teeth or mouth. Results of the Mann–Whitney test suggested that the ranked mean POQL scores were significantly higher (worse) in the fair/poor oral health group compared to the excellent/very good/good oral health group ($p = 0.01$)… In the multi-variable linear regression analysis, higher POQL score (indicating worse POQL) was associated with increased utilization of urgent dental services in the past year ($p = 0.001$).The POQL score of children who were reported to have utilized urgent dental services was 8.2 points higher than those children who had not utilized these services. OHS, child age, utilization of non-urgent dental services, and number of children in the household were not significantly associated with POQL ($p>0.05$ for all)… Caregivers who reported that their children had worse POQL were more likely to have reported them having utilized urgent dental services.
PedsQL-OH – Oral Health Scale (USA) (Steele et al. 2009)	a) 2-4; b) 5-7 c) 8-12 d) 13-18	No information found.	No studies were found that would have used PedsQL-OH specifically in preschool populations, only mixed-aged (e.g. 2 to 18 y.o.). 1) USA, English. Two samples: a) 126 families with chn aged 2-18 y. b) 34 families with chn 8-14 y.o. (Steele et al. 2009) 2) Iran, Persian: 1053 chn (8-18 y.o.) and 1026 parents. (Pakpour et al. 2011) 3) Brazil, Brazilian Portuguese:	1) Internal consistency: the parent-proxy exceeded the minimum reliability standard of 0.70, whereas the child self-reported approached this reliability criterion. Parent–Child Agreement: moderate levels. Reliability and validity supported: parent-reports exceeded the minimum alpha coefficient standard of 0.70 (i.e., 0.84), and the child self-report approached this standard (i.e., 0.68). Known-groups analysis: parent-report effectively discriminated between orally healthy and orally unhealthy children. Construct validity: Parent-report and child-report scores predicted dentist ratings of child health. Convergent validity was supported. Both parent and child reports on PedsQL-OH and COHQoL were statistically similar. (Steele et al. 2009) 2) Reliability: Cronbach's α coefficients for child-report = 0.81, parent-report = 0.89.

Instrument (Country where developed)	Age of child	Sensitivity / Responsiveness to change	Studies where the instrument was used?	Findings of studies / issues
			208 chn (2-18 y.o.) and parents (Bendo et al. 2012).	Good to excellent test-retest reliability for the scales across a 1-month test-retest interval. Construct validity was supported by the intercorrelations PedsQL-OH and PedsQL Core. PedsQL-OH effectively discriminated between children with high and low DMFT. 'Orally unhealthy' chn (DMFT>0) had significantly lower scores than 'orally healthy' (DMFT=0) (Pakpour et al. 2011) 3) Reliability: The Cronbach's alpha coefficients for child and parent instruments were 0.65 and 0.59. The test-retest reliability (ICC) for child self-report and parent proxy-report were 0.90 [95%CI = 0.86-0.93] and 0.86 (95%CI = 0.81-0.90), the test-retest interval was two weeks. Demonstrated acceptable construct validity, convergent validity and discriminant validity. Known-groups analysis: the mean score of the child-report was higher for children without dental problems (DMFT = 0) than those with dental problems (DMFT ≥ 1) ($p = 0.043$), and a similar result for parent-report ($p < 0.001$). Good agreement between the children and parents, with a value of 0.74. (Bendo et al. 2012)

Notes: YA – Yulia Anopa, ECC – early childhood caries, GA – general anaesthesia, TDI – traumatic dental injury.

References:

Abanto, J., T. S. Carvalho, F. M. Mendes, M. T. Wanderley, M. Bonecker and D. P. Raggio (2011). "Impact of oral diseases and disorders on oral health-related quality of life of preschool children." Community Dent Oral Epidemiol 39(2): 105-114.

Abanto, J., G. Tello, G. C. Bonini, L. B. Oliveira, C. Murakami and M. Bönecker (2014a). "Impact of traumatic dental injuries and malocclusions on quality of life of preschool children: a population-based study." International Journal of Paediatric Dentistry.

Abanto, J., G. Tsakos, T. M. Ardenghi, S. M. Paiva, D. P. Raggio, A. Sheiham and M. Bonecker (2013a). "Responsiveness to change for the Brazilian Scale of Oral Health Outcomes for 5-year-old children (SOHO-5)." Health Qual Life Outcomes 11(1): 137.

Abanto, J., G. Tsakos, S. M. Paiva, T. S. Carvalho, D. P. Raggio and M. Bönecker (2014b). "Impact of dental caries and trauma on quality of life among 5- to 6-year-old children: perceptions of parents and children." Community Dentistry and Oral Epidemiology.

Abanto, J., G. Tsakos, S. M. Paiva, D. Goursand, D. P. Raggio and M. Bonecker (2013b). "Cross-cultural adaptation and psychometric properties of the Brazilian version of the scale of oral health outcomes for 5-year-old children (SOHO-5)." Health Qual Life Outcomes 11: 16.

Abanto, J., G. Tsakos, S. M. Paiva, D. P. Raggio, P. Celiberti and M. Bönecker (2013c). "Agreement between children aged 5–6 years and their mothers in rating child oral health-related quality of life." International Journal of Paediatric Dentistry.

Bendo, C. B., S. M. Paiva, C. M. Viegas, M. P. Vale and J. W. Varni (2012). "The PedsQL TM Oral Health Scale: feasibility, reliability and validity of the Brazilian Portuguese version." Health & Quality of Life Outcomes 10: 42.

Braun, P. A., K. E. Lind, T. Batliner, A. G. Brega, W. G. Henderson, K. Nadeau, A. Wilson and J. Albino (2013). "Caregiver Reported Oral Health-Related Quality of Life in Young American Indian Children." J Immigr Minor Health.

Cunnion, D. T., A. Spiro, 3rd, J. A. Jones, S. E. Rich, C. P. Papageorgiou, A. Tate, P. Casamassimo, C. Hayes and R. I. Garcia (2010). "Pediatric oral health-related quality of life improvement after treatment of early childhood caries: a prospective multisite study." J Dent Child (Chic) 77(1): 4-11.

Gao, X.-L., C. McGrath and H.-C. Lin (2011). "Oral health status of rural–urban migrant children in South China." International Journal of Paediatric Dentistry 21(1): 58-67.

Huntington, N. L., D. Spetter, J. A. Jones, S. E. Rich, R. I. Garcia and A. Spiro Iii (2011). "Development and validation of a measure of pediatric oral health-related quality of life: the POQL." Journal of Public Health Dentistry 71(3): 185-193.

Klaassen, M. A., J. S. Veerkamp and J. Hoogstraten (2008). "Dental treatment under general anaesthesia: the short-term change in young children's oral-health-related quality of life." Eur Arch Paediatr Dent 9(3): 130-137.

Klaassen, M. A., J. S. Veerkamp and J. Hoogstraten (2009). "Young children's Oral Health-Related Quality of Life and dental fear after treatment under general anaesthesia: a randomized controlled trial." Eur J Oral Sci 117(3): 273-278.

Leal, S. C., E. M. Bronkhorst, M. Fan and J. E. Frencken (2012). "Untreated Cavitated Dentine Lesions: Impact on Children's Quality of Life." Caries Research 46(2): 102-106.

Leal, S. C., E. M. Bronkhorst, M. Fan and J. E. Frencken (2013). "Effect of different protocols for treating cavities in primary molars on the quality of life of children in Brazil – 1 year follow-up." International Dental Journal 63(6): 329-335.

Lee, G. H. M., C. McGrath, C. K. Y. Yiu and N. M. King (2010). "A comparison of a generic and oral health–specific measure in assessing the impact of early childhood caries on quality of life." Community Dentistry and Oral Epidemiology 38(4): 333-339.

Lee, G. H. M., C. McGrath, C. K. Y. Yiu and N. M. King (2011). "Sensitivity and responsiveness of the Chinese ECOHIS to dental treatment under general anaesthesia." Community Dentistry and Oral Epidemiology 39(4): 372-377.

Li, S., S. Malkinson, J. Veronneau and P. J. Allison (2008a). "Testing responsiveness to change for the early childhood oral health impact scale (ECOHIS)." Community Dentistry and Oral Epidemiology 36(6): 542-548.

Li, S., J. Veronneau and P. Allison (2008b). "Validation of a French language version of the Early Childhood Oral Health Impact Scale (ECOHIS)." Health and Quality of Life Outcomes 6(1): 9.

Martins-Júnior, P. A., J. Ramos-Jorge, S. M. Paiva, L. S. Marques and M. L. Ramos-Jorge (2012). "Validations of the Brazilian version of the Early Childhood Oral Health Impact Scale (ECOHIS)." Cadernos de Saúde Pública 28: 367-374.

Pahel, B., R. G. Rozier and G. Slade (2007). "Parental perceptions of children's oral health: The Early Childhood Oral Health Impact Scale (ECOHIS)." Health and Quality of Life Outcomes 5(1): 6.

Pakdaman, A., S. J. Pourhashemi, M. Bagheri Ghalesalim, S. Ghadimi and Y. Bardaran Nakhjavani (2014). "Comparison of Children's Oral Health-related quality of Life Pre- and Post Dental Treatment Under General Anesthesia Using F-ECOHIS Questionnaire." 2013 24(1): 121-122.

Pakpour, A. H., M. S. Yekaninejad, F. Zarei, F. Hashemi, M. M. Steele and J. W. Varni (2011). "The PedsQL TM Oral Health Scale in Iranian children: reliability and validity." International Journal of Paediatric Dentistry 21(5): 342-352.

Steele, M. M., R. G. Steele and J. W. Varni (2009). "Reliability and Validity of the PedsQL™ Oral Health Scale: Measuring the Relationship Between Child Oral Health and Health-Related Quality of Life." Children's Health Care 38(3): 228-244.

Tsakos, G. (2010). Oral health-related quality of life (OHRQoL) measurement in 5-year-olds in Glasgow: developing and evaluating a new OHRQoL measure: final report. London, University College London.

Tsakos, G., Y. I. Blair, H. Yusuf, W. Wright, R. G. Watt and L. M. Macpherson (2012). "Developing a new self-reported scale of oral health outcomes for 5-year-old children (SOHO-5)." Health Qual Life Outcomes 10: 62.

Wong, H. M., C. P. J. McGrath, N. M. King and E. C. M. Lo (2011). "Oral Health-Related Quality of Life in Hong Kong Preschool Children." Caries Research 45(4): 370-376.

Appendix 15 PT@3 Study: parental questionnaire

Protecting Teeth @ 3

NHS SCOTLAND

(R3)

How does a child's health affect their quality of life?

We would like to ask you the same series of questions as we asked you a year and two years ago, in order to find out how a child's oral and general health affect their quality of life. The questionnaire takes around 10 to 15 minutes to fill in. Some questions might seem to cover the same ground, but they do serve slightly different purposes, so please answer all questions in this questionnaire pack.

Like your child's involvement in the main Protecting Teeth @ 3 Study, participation in this survey is voluntary. If you decide not to complete the questionnaire, your decision will not affect your child's continued participation in the study, or the standard of care you or your child may receive from the NHS, now or in the future. Your answers will be treated confidentially.

This is the third and final round of this questionnaire. Even though you may have filled earlier versions, we need you to fill in this one as well to help us to assess if there have been any changes over time.

If you would like more information you can contact us on: 0141 211 9853 or 0141 211 9802.

PLEASE ANSWER ALL QUESTIONS IN THIS PACK, THEN POST IT BACK TO US IN THE PRE-PAID ENVELOPE PROVIDED.

As a thank you for helping us, we are offering you the chance to enter a free prize draw to win an iPad. Each time you fill in a questionnaire you have a chance of winning. Please tick the most appropriate box below:

Yes, I would like to take part in the draw ☐

No, I do not want to take part in the draw ☐

In order to be included in the draw you must return your completed questionnaires within 28 days.

OFFICE USE ONLY	
Participant's ID:	
Date received:	Date entered onto database:
Received by (initials):	*Entered by (initials):*

The University Of Sheffield.

Child Health Utility 9D

Instructions

These questions ask about how your child is **today.** For each question, read all the choices and decide which one is most like your child **today**.

Then put a tick in the box next to it like this ☑. Only tick **one** box for each question. Some questions have extra guidance with them as your child is under 5 years of age.

Example
Today my child feels quite upset so I will tick this box.

Upset
- ☐ My child doesn't feel upset today
- ☐ My child feels a little bit upset today
- ☐ My child feels a bit upset today
- ☑ My child feels quite upset today
- ☐ My child feels very upset today

Now think about and answer the rest of the questions below

1. Worried
- ☐ My child doesn't feel worried today
- ☐ My child feels a little bit worried today
- ☐ My child feels a bit worried today
- ☐ My child feels quite worried today
- ☐ My child feels very worried today

2. Sad
- ☐ My child doesn't feel sad today
- ☐ My child feels a little bit sad today
- ☐ My child feels a bit sad today
- ☐ My child feels quite sad today
- ☐ My child feels very sad today

3. Pain

- ☐ My child doesn't have any pain today
- ☐ My child has a little bit of pain today
- ☐ My child has a bit of pain today
- ☐ My child has quite a lot of pain today
- ☐ My child has a lot of pain today

4. Tired

- ☐ My child doesn't feel tired today
- ☐ My child feels a little bit tired today
- ☐ My child feels a bit tired today
- ☐ My child feels quite tired today
- ☐ My child feels very tired today

5. Annoyed

- ☐ My child doesn't feel annoyed today
- ☐ My child feels a little bit annoyed today
- ☐ My child feels a bit annoyed today
- ☐ My child feels quite annoyed today
- ☐ My child feels very annoyed today

6. School Work/Homework (such as reading, writing, doing lessons)

If your child is at preschool/nursery/kindergarten then please think about that. If your child didn't go today because of their health and they usually would have, please tick the last option "My child can't do their schoolwork/homework today". If today is not a day they usually would have gone, then please think about how you think they would have been had they gone. If your child does not go to preschool/nursery/kindergarten, then please think about whether they have had any problems with activities such as colouring, looking at books/reading, and concentrating, as appropriate for their age.

- ☐ My child has no problems with their schoolwork/homework today
- ☐ My child has a few problems with their schoolwork/homework today
- ☐ My child has some problems with their schoolwork/homework today
- ☐ My child has many problems with their schoolwork/homework today
- ☐ My child can't do their schoolwork/homework today

7. Sleep

- ☐ Last night my child had no problems sleeping
- ☐ Last night my child had a few problems sleeping
- ☐ Last night my child had some problems sleeping
- ☐ Last night my child had many problems sleeping
- ☐ Last night my child couldn't sleep at all

8. Daily routine (things like eating, having a bath/shower, getting dressed)

Please think about this question in terms of eating, drinking, toileting, washing and teeth cleaning, as appropriate for their age.

- ☐ My child has no problems with their daily routine today
- ☐ My child has a few problems with their daily routine today
- ☐ My child has some problems with their daily routine today
- ☐ My child has many problems with their daily routine today
- ☐ My child can't do their daily routine today

9. Able to join in activities (things like playing out with their friends, doing sports, joining in things)

Please think about this question in terms of the activities your child would usually be doing today.

- ☐ My child can join in with any activities today
- ☐ My child can join in with most activities today
- ☐ My child can join in with some activities today
- ☐ My child can join in with a few activities today
- ☐ My child can join in with no activities today

10. How would you rate your child's health today?

- ☐ excellent
- ☐ very good
- ☐ good
- ☐ fair
- ☐ poor

11. Do you feel there is any aspect of your child's health related quality of life that is not covered by these questions?

_____

_____

_____

_____

_____

PedsQL™

Pediatric Quality of Life Inventory

Version 4.0

PARENT REPORT for **TODDLERS** (ages **2-4**)

DIRECTIONS

On the following page is a list of things that might be a problem for **your child**. Please tell us **how much of a problem** each one has been for **your child** during the **past ONE month** by circling:

0 if it is **never** a problem
1 if it is **almost never** a problem
2 if it is **sometimes** a problem
3 if it is **often** a problem
4 if it is **almost always** a problem

There are no right or wrong answers.
If you do not understand a question, please ask for help.

*In the past **ONE month,** how much of a **problem** has your child had with …*

PHYSICAL FUNCTIONING *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. Walking	0	1	2	3	4
2. Running	0	1	2	3	4
3. Participating in active play or exercise	0	1	2	3	4
4. Lifting something heavy	0	1	2	3	4
5. Bathing	0	1	2	3	4
6. Helping to pick up his or her toys	0	1	2	3	4
7. Having hurts or aches	0	1	2	3	4
8. Low energy level	0	1	2	3	4

EMOTIONAL FUNCTIONING *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. Feeling afraid or scared	0	1	2	3	4
2. Feeling sad or blue	0	1	2	3	4
3. Feeling angry	0	1	2	3	4
4. Trouble sleeping	0	1	2	3	4
5. Worrying	0	1	2	3	4

SOCIAL FUNCTIONING *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. Playing with other children	0	1	2	3	4
2. Other kids not wanting to play with him or her	0	1	2	3	4
3. Getting teased by other children	0	1	2	3	4
4. Not able to do things that other children his or her age can do	0	1	2	3	4
5. Keeping up when playing with other children	0	1	2	3	4

Please complete this section if your child attends school or daycare

SCHOOL FUNCTIONING *(problems with...)*	Never	Almost Never	Some-times	Often	Almost Always
1. Doing the same school activities as peers	0	1	2	3	4
2. Missing school/daycare because of not feeling well	0	1	2	3	4
3. Missing school/daycare to go to the doctor or hospital	0	1	2	3	4

*In the past **ONE month,** how much of a **problem** has your child had with …*

ABOUT MY CHILD'S TEETH AND MOUTH *(problems with…)*	Never	Almost Never	Some-times	Often	Almost Always
1. Having tooth pain	0	1	2	3	4
2. Having tooth pain when eating or drinking something hot, cold, or sweet	0	1	2	3	4
3. Having teeth that are dark in color	0	1	2	3	4
4. Having gum pain	0	1	2	3	4
5. Having blood on his or her toothbrush after brushing	0	1	2	3	4

University of Glasgow UCL

The Scale of Oral Health Outcomes for children (SOHO-5)

Questions about your child's dental health and the effect of your child's teeth on his/her daily life

Now we would like to know more about your child's teeth and mouth and how they affect their daily life. Please **tick** the most appropriate response on the scale below.

In the <u>PAST 12 MONTHS</u> has you child:

1. Had any difficulty **eating** because of his/her teeth?

☐ not at all ☐ a little ☐ moderate ☐ a lot ☐ a great deal ☐ don't know

2. Had any difficulty **speaking** because of his/her teeth?

☐ not at all ☐ a little ☐ moderate ☐ a lot ☐ a great deal ☐ don't know

3. Had any difficulty **playing** because of his/her teeth?

☐ not at all ☐ a little ☐ moderate ☐ a lot ☐ a great deal ☐ don't know

4. Avoided **smiling** because of the **appearance** of his/her teeth?

☐ not at all ☐ a little ☐ moderate ☐ a lot ☐ a great deal ☐ don't know

5. Avoided **smiling** because of the **state (holes in teeth, pain)** of his/her teeth?

☐ not at all ☐ a little ☐ moderate ☐ a lot ☐ a great deal ☐ don't know

6. Had difficulty **sleeping** because of his/her teeth?

☐ not at all ☐ a little ☐ moderate ☐ a lot ☐ a great deal ☐ don't know

7. Has your child's **self-confidence** been affected because of his/her teeth (in the past 12 months)?

☐ not at all ☐ a little ☐ moderate ☐ a lot ☐ a great deal ☐ don't know

University of Glasgow

OVERALL CHANGES IN YOUR CHILD'S HEALTH
in the past 12 months

a) How did your child's <u>GENERAL HEALTH</u> change in the PAST 12 MONTHS? *(Tick one)*

☐ Worsened a lot	☐ Worsened a little	☐ Stayed the same	☐ Improved a little	☐ Improved a lot

b) How did your child's <u>ORAL HEALTH</u> change in the PAST 12 MONTHS? *(Tick one)*

☐ Worsened a lot	☐ Worsened a little	☐ Stayed the same	☐ Improved a little	☐ Improved a lot

YOUR CHILD'S USE OF HEALTH AND DENTAL CARE SERVICES in the past 12 months

1) What health and dental care services has your child used within the PAST 12 MONTHS?

Note: Please enter '0' (zero) if service has not been used

Service	Total number of contacts
General Practitioner (GP)	
Accident and Emergency (A&E) visit	
Dentist (at your family dental practice)	
Dental hygienist / therapist (at your family dental practice)	
Speech therapist	
Hospital inpatient stay	Number of nights: _____
Hospital outpatient stay	
Other (1): _____	
Other (2): _____	

2) Please list below your child's use of any medication (e.g. pain-killers, antibiotics) he/she has taken within the PAST 12 MONTHS:

Name of medication	How long did your child take this medication for? (for example, '3 days' or '1 week')	Daily dosage
1.		
2.		
3.		
4.		
5.		

3) In the past 12 months, approximately how many days has your child had off nursery/school due to ill health (including ill health due to dental problems)?

Number of days off nursery/school: ☐

4) Did you or other parent/guardian have to take time off work or your usual daily activities due to your child being off nursery/school (due to ill health) in the past 12 months?

Yes ☐ *No* ☐ *(tick one)* If yes, please state how many days: ☐

This is the end of the questionnaire

THANK YOU VERY MUCH!

Now please post this questionnaire back to us in the pre-paid envelope provided

Appendix 16 PT@3 Study: staff costs questionnaire

Protecting Teeth @ 3 Study: Costs to the NHS

(Fluoride Varnish / Treatment as Usual Visit)

This questionnaire should be completed by one intervention team member (ideally the team lead) on behalf of all team members present on the Fluoride Varnish / Treatment as Usual Visit. *(If a baseline dental inspection is happening on the same visit, do NOT include the details of the inspecting dentist and the scribe.)*

The purpose of collecting this information is to calculate the costs incurred by the NHS in regard to the PT@3 Study and relate these to the outcomes in the participants' d_3mft at the end of the trial.

Please complete a questionnaire for each nursery school visited, even if visits occurred on the same day.

Please fill in the questionnaire using ink and block capitals.

Section 1

Nursery name:	**Date of Visit:**
_____	_____

Section 2 – Staff travel

In this section we need to collect information on how *all* intervention team members travelled to and from this nursery. Where staff shared transport please list all team members who travelled together in column c) in the table below

a) All staff journeys to / from this nursery		b) Mode of transport (van, car, bus, train, if other please specify)	c) Names & Surnames of team members who shared this journey	Travel TO this nursery		Travel FROM this nursery	
				d) Postcode of origin of your work-related travel	e) Approx. mileage	f) Postcode of destination (where you are going after this nursery visit)	g) Approx. mileage to this destination
Ex1	am (circled) / pm	*Childsmile van*	*Mary Poppins, Sue Barton*	*G2 3JZ*	*5 miles*	*G21 2DA*	*4 miles*
Ex2	am (circled) / pm	*Bus*	*Jane Bloggs (travelled alone)*	*G34 9HQ*	*2 miles*	*G34 9HQ*	*2 miles*
1	am / pm						
2	am / pm						
3	am / pm						
4	am / pm						
5	am / pm						
6	am / pm						
7	am / pm						

Section 3 – Intervention (Fluoride Varnish / TAU) day

What PT@3 activities were undertaken during **this** nursery visit? (Please **tick all** that apply):

- ☐ Baseline dental inspections
- ☐ Randomisations
- ☐ Interventions (fluoride varnishing / treatment as usual)

Morning session	Afternoon session
a) When did the first intervention team member **arrive** at the nursery (**AM**)? _____hh _____mm *(**Example:** 8:40am)*	c) When did the first intervention team member **arrive** at the nursery (**PM**)? _____hh _____mm *(**Example:** 13:00 or 1:00pm)*
b) When all the intervention activities were completed, when did the last intervention team member **leave** the nursery (before going elsewhere)? _____hh _____mm *(**Example:** 11:35am)*	d) When all the intervention activities were completed, when did the last intervention team member **leave** the nursery? _____hh _____mm *(**Example:** 14:30 or 2:30pm)*
If you did not leave the nursery between the morning and afternoon sessions, indicate only one set of times: e.g. *arrived at 8:40am, left at 14:30*	

Section 4 – Do you have any additional comments in relation to this nursery visit?

Thank you very much!

Please file the completed form in the relevant nursery PT@3 folder at the end of the day

Appendix 17 Missing data for the resource use items in the intervention and control groups

Variable	FV (intervention) No. of missing	%	TAU (control) No. of missing	%
Baseline				
GP	79	29.9%	70	26.0%
A&E	77	29.2%	65	24.2%
Dentist	81	30.7%	70	26.0%
Hygienist (dental)	75	28.4%	67	24.9%
Speech therapist	77	29.2%	68	25.3%
Inpatient stay	76	28.8%	65	24.2%
Outpatient stay	76	28.8%	65	24.2%
12-month				
GP	118	44.7%	110	40.9%
A&E	117	44.3%	107	39.8%
Dentist	118	44.7%	111	41.3%
Hygienist (dental)	116	43.9%	106	39.4%
Speech therapist	116	43.9%	106	39.4%
Inpatient stay	116	43.9%	106	39.4%
Outpatient stay	116	43.9%	106	39.4%
24-month				
GP	117	44.3%	110	40.9%
A&E	117	44.3%	111	41.3%
Dentist	117	44.3%	110	40.9%
Hygienist (dental)	117	44.3%	111	41.3%
Speech therapist	117	44.3%	111	41.3%
Inpatient stay	117	44.3%	111	41.3%
Outpatient stay	117	44.3%	111	41.3%

Appendix 18 Missing data for the resource use, CHU9D-based utility scores and d3mft in the intervention and control groups

Data items	Intervention - FV (n=265)		Control - TAU (n=269)	
	No. of missing	%	No. of missing	%
Resource use				
Baseline: Sum of listed resource use items	0	0	0	0
Baseline: "Other" resource use items	0	0	0	0
12-mo: Sum of listed resource use items	117	44.2	105	39.0
12-mo: "Other" resource use items	117	44.2	105	39.0
24-mo: Sum of listed resource use items	118	44.5	110	40.9
24-mo: "Other" resource use items	118	44.5	110	40.9
Utility				
Baseline utility	0	0	0	0
12-mo utility	117	44.2	110	40.9
24-mo utility	118	44.5	112	41.6
d3mft				
Baseline d3mft	1	0.4	2	0.7
24-mo d3mft	9	3.4	16	6.0

Note: This is the level at which multiple imputations were performed, i.e. after the mean imputation of baseline values and mean imputation of single missing recourse use items (as opposed to a non-returned questionnaire or a whole section of a questionnaire not filled in) had been conducted.

Appendix 19 Unit costs for "other" resource use items

Item	Unit cost	Source
Allergy Clinic	£197.94	NHS National schedule of reference costs - the main schedule, 2016/17. 'Total Outpatient Attendances', 255, Paediatric Clinical Immunology and Allergy Service.
Asthma outpatient clinic	£112.20	NHS National schedule of reference costs - the main schedule, 2016/17. 'Total Other Currencies' tab, N08CF, Specialist Nursing, Asthma and Respiratory Nursing/Liaison, Child, Face to face.
Audiology	£86.83	NHS National schedule of reference costs - the main schedule, 2016/17. 'Total Outpatient Attendances', 840, Audiology.
Children's ward - high temp	£397.90	Costed as a one-night inpatient stay.
Childsmile	£15.22	Assumed it's Childsmile delivered by a dentist. Took 350 seconds to deliver the intervention (Yuan et al, 2019 - submitted to BDJ in March 2019)
Childsmile Nurse	£3.13	Assumed it's Childsmile at a dental practice, delivered by a dental nurse. Took 1015 seconds to deliver the intervention (Yuan et al, 2019 - submitted to BDJ in March 2019).
Dental hospital	£125.39	NHS National schedule of reference costs - the main schedule, 2016/17. 'Total Outpatient Attendances', 142, Paediatric Dentistry.
Dermatology	£147.90	NHS National schedule of reference costs - the main schedule, 2016/17. 'Total Outpatient Attendances', 257, Paediatric Dermatology.
Dietician	£84.85	NHS National schedule of reference costs - the main schedule, 2016/17. 'Total Other Currencies', A03, Dietitian.
Edinburgh Cleft Team	£195.54	NHS National schedule of reference costs - the main schedule, 2016/17. 'Total Outpatient Attendances', 217, Paediatric Maxillo-Facial Surgery.
Eye-test related (various wording: eye clinic, eye hospital, eye outpatient clinic, eye test, optician, given glasses, etc.)	£66.30	NHS National schedule of reference costs - the main schedule, 2016/17. 'Total Outpatient Attendances', 662, Optometry.
Health centre	£37.00	Costed as a GP visit cost.
Health visitor	£54.65	NHS National schedule of reference costs - the main schedule, 2016/17. 'Total Other Currencies' tab, N03F - Health Visitor, Other Clinical Intervention.
Health visitor - vaccination	£22.59	NHS National schedule of reference costs - the main schedule, 2016/17. 'Total Other Currencies' tab, N03N - Health Visitor, Immunisation.
Hospital Dietician	£84.85	NHS National schedule of reference costs - the main schedule, 2016/17. 'Total Other Currencies', A03, Dietitian.

Item	Unit cost	Source
NHS 24 - out of hours (assumed: out of hours GP visit)	£71.07	Report on out-of-hours GP services in England by National Audit Office 2013–14, pp. 15–16 (£68.30). Inflated to 2016/17 level it is £71.07 https://www.nao.org.uk/wp-content/uploads/2014/09/Out-of-hours-GP-services-in-England1.pdf [Accessed: 28/03/2019]
NHS24 phone call	£7.90	PSSRU 2017 p. 164, Table 10.4 Telephone triage – GP-led and nurse-led. Item 'Cost per intervention including other costs'
Nurse	£21.00	PSSRU 2017 p.160, Nurse (GP practice) = £42 per hour. Assuming it took 30min = £21 per contact.
Orthoptics	£64.03	NHS National schedule of reference costs - the main schedule, 2016/17. 'Total Outpatient Attendances', 655, Orthoptics.
Paediatrician	£198.20	NHS reference cost 2016/17 main schedule, Tab 'Total Outpatient Attendances', service code 420 – Paediatrics.
Physio	£94.62	NHS National schedule of reference costs - the main schedule, 2016/17. 'Total Other Currencies' tab, A08C1 - Physiotherapist, Child, One to One.
Plastic surgeon	£100.72	NHS National schedule of reference costs - the main schedule, 2016/17. 'Total Outpatient Attendances', 160, Plastic Surgery.
Play therapy	£50.00	Play Therapy UK (PTUK) website. Guidance on Remuneration Scales, PTUK Remuneration Guidelines; Midpoint value - Play Therapist newly qualified (200 hours). https://playtherapy.org.uk/CareersInPlayTherapy/CareerAdvice/Remuneration [Accessed 28/03/2019]
Routine consultant appointment (Assumption: Gastroenterology)	£226.86	Assumed it has something to do with reflux. NHS National schedule of reference costs - the main schedule, 2016/17. 'Total Outpatient Attendances', 251, Paediatric Gastroenterology
Tissue viability clinic	£69.42	NHS National schedule of reference costs - the main schedule, 2016/17. 'Total other currencies', N25CF, Specialist Nursing, Tissue Viability Nursing/Liaison, Child, Face to face.
Yorkhill Children's Hospital	£198.20	Costed as an outpatient stay.

Appendix 20 Endpoint analysis of the economic evaluation sample

Endpoint	FV		TAU					
	n	(%)	n	(%)	OR	95% CI		P
Total No of participants with available 0 mo. and 24 mo. d3mft data (100%) *	255*	(100%)	253*	(100%)				
Worse d3mft	74	(29%)	79	(31%)	0.90	(0.62,	1.32)	0.588

Note: EE – economic evaluation, d3mft – number of teeth decayed into dentine (d3), missing (m), and filed (f) teeth (t).

* There were no 24-month and/or 0-month d3mft data available for 26 children, due to missing / ineligible dental inspection information.

Appendix 21 Number needed to treat and relevant cost

The number needed to treat (NNT) and the related cost to treat these children were calculated. The NNT is the average number of patients who need to receive the treatment or other intervention for one of them to get the positive outcome in the time specified. The closer the NNT is to 1, the more effective the treatment (NICE 2020).

The formulae used to calculate the NNT and the related cost are presented in Table 5.9. First, we calculated the absolute risk (AR) for each study group, which is the number of events (in this case the children with worsened d3mft) in the intervention or control groups, divided by the number of people in that group. Then we calculated the absolute risk reduction (ARR), which is the difference between the AR of the standard treatment, in this case TAU, and the AR of the new treatment, in this case FV (ARR = ARTAU - ARFV) (BMJ Best Practice 2020). The number needed to treat is simply the reciprocal of the ARR, or 1/ARR (or 100/ARR if percentages are used rather than proportions) (Altman 1998). Further, to calculate the cost of preventing one child from having a worsening of d3mft, the mean intervention cost per child in the FV group was multiplied by the NNT (BI = CInt FV * NNT).

References:

Altman, D. G. (1998). "Confidence intervals for the number needed to treat." Bmj 317(7168): 1309-1312.

BMJ Best Practice. (2020). "EBM (Evidence-based Medicine) Toolkit » Learn EBM » How to calculate risk." Retrieved 4th March, 2020, from https://bestpractice.bmj.com/info/toolkit/learn-ebm/how-to-calculate-risk/.

NICE. (2020). "The NICE glossary." Retrieved 2nd March, 2020, from https://www.nice.org.uk/glossary

Results of number needed to treat cost calculation

Treatment group	Children with worsened d3mft (n)	Total in group (N)	AR (= n / N)	ARR (= AR_{TAU} - AR_{FV})	NNT (=1/ARR)	Cost, £ (= $C_{Int\ FV}$ * NNT)
FV	74	255*	0.290	0.022	45	1,469.70
TAU	79	253*	0.312			

Notes: AR – absolute risk, ARR – absolute risk reduction, NNT – number needed to treat, $C_{Int\ FV}$ – mean intervention cost per FV group child (£32.66).

* The dental effectiveness (d3mft) data were missing/ineligible for 26 children: 10 in the FV group and 16 in the TAU group. Hence, Ns were lower than in the overall EE sample.

List of References

Abanto, J., T. S. Carvalho, F. M. Mendes, M. T. Wanderley, M. Bonecker and D. P. Raggio (2011). "Impact of oral diseases and disorders on oral health-related quality of life of preschool children." Community Dent Oral Epidemiol **39**(2): 105-114.

Abanto, J., G. Tsakos, S. M. Paiva, D. P. Raggio, P. Celiberti and M. Bönecker (2013a). "Agreement between children aged 5–6 years and their mothers in rating child oral health-related quality of life." International Journal of Paediatric Dentistry: n/a-n/a.

Abanto, J., G. Tsakos, S. M. Paiva, D. Goursand, D. P. Raggio and M. Bonecker (2013b). "Cross-cultural adaptation and psychometric properties of the Brazilian version of the scale of oral health outcomes for 5-year-old children (SOHO-5)." Health Qual Life Outcomes **11**: 16.

Abanto, J., G. Tsakos, T. M. Ardenghi, S. M. Paiva, D. P. Raggio, A. Sheiham and M. Bonecker (2013c). "Responsiveness to change for the Brazilian Scale of Oral Health Outcomes for 5-year-old children (SOHO-5)." Health Qual Life Outcomes **11**(1): 137.

Abanto, J., G. Tsakos, S. M. Paiva, T. S. Carvalho, D. P. Raggio and M. Bönecker (2014a). "Impact of dental caries and trauma on quality of life among 5- to 6-year-old children: perceptions of parents and children." Community Dentistry and Oral Epidemiology: n/a-n/a.

Abanto, J., G. Tello, G. C. Bonini, L. B. Oliveira, C. Murakami and M. Bönecker (2014b). "Impact of traumatic dental injuries and malocclusions on quality of life of preschool children: a population-based study." International Journal of Paediatric Dentistry: n/a-n/a.

Allen, P. F. (2003). "Assessment of oral health related quality of life." Health and Quality of Life Outcomes **1**(1): 40.

American Academy of Pediatric Dentistry (2019). Caries risk assessment and management for infants, children, and adolescents. Reference Manual.

Amilani, U., H. E. Carter, S. Senanayake, R. M. Hettiarachchi, S. M. McPhail and S. Kularatna (2020). "A scoping review of cost-effectiveness analyses of school-based interventions for caries." Community Dentistry and Oral Epidemiology **48**(5): 357-363.

Anderson, M., T. Davidson, G. Dahllof and M. Grindefjord (2019). "Economic evaluation of an expanded caries-preventive program targeting toddlers in high-risk areas in Sweden." Acta Odontol Scand **77**(4): 303-309.

Anell, A. and A. Norinder (2000). "Health outcome measures used in cost-effectiveness studies: a review of original articles published between 1986 and 1996." Health Policy **51**(2): 87-99.

Anil, S. and P. S. Anand (2017). "Early Childhood Caries: Prevalence, Risk Factors, and Prevention." Frontiers in Pediatrics **5**(157).

Anopa, Y., A. D. McMahon, D. I. Conway, G. E. Ball, E. McIntosh and L. M. Macpherson (2015). "Improving Child Oral Health: Cost Analysis of a National Nursery Toothbrushing Programme." PLoS One **10**(8): e0136211.

Anopa, Y., L. Macpherson and E. McIntosh. (2017). "Economic evaluations of paediatric caries prevention in pre-school children aged two to five years: a systematic review. PROSPERO 2017, CRD42017083732." Retrieved August, 2018, from http://www.crd.york.ac.uk/PROSPERO/display_record.php?ID=CRD42017083732.

Anopa, Y., L. Macpherson and E. McIntosh (2020). "Systematic Review of Economic Evaluations of Primary Caries Prevention in 2- to 5-Year-Old Preschool Children." Value in Health.

Appleby, J. (2013). "Spending on health and social care over the next 50 years." Why think long term **10**.

Ast, D. B., N. C. Cons, J. P. Carlos and A. Maiwald (1965). "Time and Cost Factors to Provide Regular, Periodic Dental Care for Children in a Fluoridated and Nonfluoridated Area." American Journal of Public Health and the Nations Health **55**(6): 811-820.

Ast, D. B., N. C. Cons, J. P. Carlos and A. Polan (1967). "Time and cost factors to provide regular, periodic dental care for children in a fluoridated and nonfluoridated area: progress report. II." Am J Public Health Nations Health **57**(9): 1635-1642.

Ast, D. B., N. C. Cons, S. T. Pollard and J. Garfinkel (1970). "Time and cost factors to provide regular, periodic dental care for children in a fluoridated and nonfluoridated area: final report." J Am Dent Assoc **80**(4): 770-776.

Atala-Acevedo, C., C. Zaror, G. Espinoza-Espinoza, P. Muñoz-Millán, S. Muñoz, M. J. Martínez-Zapata and M. Ferrer (2020). "Adaptation and validation of the PEDSQL™ oral health scale for toddlers in Chilean population." BMC Oral Health **20**(1): 6.

Ataniyazova, R., J. Negmatov and Z. Parpiev (2014). "A Cost-Benefit Analysis of Early Childhood Hygiene Interventions in Uzbekistan." Eurasian Journal of Business and Economics **7**(14): 183-208.

Atkins, C. Y., T. K. Thomas, D. Lenaker, G. M. Day, T. W. Hennessy and M. I. Meltzer (2016). "Cost-effectiveness of preventing dental caries and full mouth dental reconstructions among Alaska Native children in the Yukon-Kuskokwim delta region of Alaska." J Public Health Dent **76**(3): 228-240.

BaniHani, A., C. Deery, J. Toumba, T. Munyombwe and M. Duggal (2018). "The impact of dental caries and its treatment by conventional or biological approaches on the oral health-related quality of life of children and carers." International Journal of Paediatric Dentistry **28**(2): 266-276.

Banke-Thomas, A. O., B. Madaj, A. Charles and N. van den Broek (2015). "Social Return on Investment (SROI) methodology to account for value for money of public health interventions: a systematic review." BMC Public Health **15**(1): 582.

Barber, J. and S. Thompson (2004). "Multiple regression of cost data: use of generalised linear models." Journal of health services research & policy **9**(4): 197-204.

Barbosa, T. S. and M. B. Gaviao (2008a). "Oral health-related quality of life in children: part I. How well do children know themselves? A systematic review." Int J Dent Hyg **6**(2): 93-99.

Barbosa, T. S. and M. B. Gaviao (2008b). "Oral health-related quality of life in children: part II. Effects of clinical oral health status. A systematic review." Int J Dent Hyg **6**(2): 100-107.

Barbosa, T. S. and M. B. Gaviao (2008c). "Oral health-related quality of life in children: part III. Is there agreement between parents in rating their children's oral health-related quality of life? A systematic review." Int J Dent Hyg **6**(2): 108-113.

Bendo, C. B., S. M. Paiva, C. M. Viegas, M. P. Vale and J. W. Varni (2012). "The PedsQL TM Oral Health Scale: feasibility, reliability and validity of the Brazilian Portuguese version." Health & Quality of Life Outcomes **10**: 42.

Bennadi, D. and C. V. K. Reddy (2013). "Oral health related quality of life." Journal of International Society of Preventive & Community Dentistry **3**(1): 1-6.

Bergström, E. K., T. Davidson and U. Moberg Sköld (2019). "Cost-Effectiveness through the Dental-Health FRAMM Guideline for Caries Prevention among 12- to 15-Year-Olds in Sweden." Caries Research **53**(3): 339-346.

Berkowitz, R. J. (2003). "Causes, treatment and prevention of early childhood caries: a microbiologic perspective." Journal-Canadian Dental Association **69**(5): 304-307.

Birch, S. and C. Donaldson (1987). "Applications of cost-benefit analysis to health care: Departures from welfare economic theory." Journal of Health Economics **6**(3): 211-225.

Birch, S. and S. Listl (2015). "The economics of oral health and health care." Max Planck Institute for Social Law and Social Policy Discussion Paper(07-2015).

Borutta, A., G. Reuscher, S. Hufnagl and S. Möbius (2006). "Caries prevention with fluoride varnishes among preschool children." Gesundheitswesen (Bundesverband der Arzte des Offentlichen Gesundheitsdienstes (Germany)) **68**(11): 731-734.

Bradlyn, A. S., A. K. Ritchey, C. V. Harris, I. M. Moore, R. T. O'Brien, S. K. Parsons, K. Patterson and B. H. Pollock (1996). "Quality of life research in pediatric oncology: research methods and barriers." Cancer: Interdisciplinary International Journal of the American Cancer Society **78**(6): 1333-1339.

Bramer, W. M., J. Milic and F. Mast (2017). "Reviewing retrieved references for inclusion in systematic reviews using EndNote." Journal of the Medical Library Association : JMLA **105**(1): 84-87.

Braun, P. A., K. E. Lind, T. Batliner, A. G. Brega, W. G. Henderson, K. Nadeau, A. Wilson and J. Albino (2013). "Caregiver Reported Oral Health-Related Quality of Life in Young American Indian Children." J Immigr Minor Health.

Brazier, J., J. Roberts and M. Deverill (2002). "The estimation of a preference-based measure of health from the SF-36." J Health Econ **21**(2): 271-292.

Brazier, J. and L. Longworth (2011). NICE DSU Technical Support Document 8: An introduction to the measurement and valuation of health for NICE submissions. Sheffield, UK, Decision Support Unit.

Brazier, J., J. Ratcliffe, J. Saloman and A. Tsuchiya (2016). Measuring and valuing health benefits for economic evaluation, OXFORD university press.

Brazier, J., R. Ara, D. Rowen and H. Chevrou-Severac (2017). "A Review of Generic Preference-Based Measures for Use in Cost-Effectiveness Models." PharmacoEconomics **35**(1): 21-31.

Brewster, L., A. Sherriff and L. Macpherson (2013). "Effectiveness and reach of a directed-population approach to improving dental health and reducing inequalities: a cross sectional study." BMC Public Health **13**(1): 778.

Briggs, A. and M. Tambour (2001). "The design and analysis of stochastic cost-effectiveness studies for the evaluation of health care interventions." Drug information journal : DIJ / Drug Information Association **35**(4): 1455-1468.

Briggs, A. H., D. E. Wonderling and C. Z. Mooney (1997). "Pulling cost-effectiveness analysis up by its bootstraps: a non-parametric approach to confidence interval estimation." Health economics **6**(4): 327-340.

Briggs, A. H. and B. J. O'Brien (2001). "The death of cost-minimization analysis?" Health Economics **10**(2): 179-184.

Briggs, A. H. (2004). "Statistical approaches to handling uncertainty in health economic evaluation." European Journal of Gastroenterology & Hepatology **16**(6).

Briggs, A. H., K. Claxton and M. J. Sculpher (2006). Decision Modelling for Health Economic Evaluation, Oxford University Press, USA.

Briggs, A. H., M. C. Weinstein, E. A. L. Fenwick, J. Karnon, M. J. Sculpher and A. D. Paltiel (2012). "Model Parameter Estimation and Uncertainty: A Report of the ISPOR-SMDM Modeling Good Research Practices Task Force-6." Value in Health **15**(6): 835-842.

Brousselle, A., T. Benmarhnia and L. Benhadj (2016). "What are the benefits and risks of using return on investment to defend public health programs?" Preventive Medicine Reports **3**: 135-138.

Buck, D. (2012). "The PedsQL™ as a measure of parent-rated quality of life in healthy UK toddlers: Psychometric properties and cross-cultural comparisons." Journal of Child Health Care **16**(4): 331-338.

Buck, D. (2018). "Talking about the 'return on investment of public health': why it's important to get it right." The King's Fund blog https://www.kingsfund.org.uk/blog/2018/04/return-investment-public-health#comments-top Accessed September 2020 2020.

Buckingham, S. and J. H. John (2017). "Outcomes and costs of pre-school and school-based fluoride varnish pilots." British Dental Journal **222**(8): 591-594.

Bulamu, N. B., B. Kaambwa and J. Ratcliffe (2015). "A systematic review of instruments for measuring outcomes in economic evaluation within aged care." Health Qual Life Outcomes **13**: 179.

CADTH. (2016). "Strings Attached: CADTH's Database Search Filters." Retrieved August, 2018, from https://www.cadth.ca/resources/finding-evidence/strings-attached-cadths-database-search-filters#eco.

Canaway, A. G. and E. J. Frew (2013). "Measuring preference-based quality of life in children aged 6–7 years: a comparison of the performance of the CHU-9D and EQ-5D-Y—the WAVES Pilot Study." Quality of Life Research **22**(1): 173-183.

Cannon, P. (2017). "Personal profile on the University of Glasgow webpage." Retrieved August, 2018, from https://www.gla.ac.uk/myglasgow/library/contact/libstafflist/collegelibrarians/paulcannon/.

Carey, C. M. (2014). "Focus on Fluorides: Update on the Use of Fluoride for the Prevention of Dental Caries." Journal of Evidence Based Dental Practice **14**: 95-102.

Casamassimo, P. S., S. Thikkurissy, B. L. Edelstein and E. Maiorini (2009). "Beyond the dmft: the human and economic cost of early childhood caries." J Am Dent Assoc **140**(6): 650-657.

Centre for Reviews and Dissemination (2008). Systematic Reviews. CRD's guidance for undertaking reviews in health care. York, University of York.

Chaplin, J. E., H. M. Koopman, S. Schmidt and D. Group (2008). "DISABKIDS smiley questionnaire: the TAKE 6 assisted health-related quality of life measure for 4 to 7-year-olds." Clinical psychology & psychotherapy **15**(3): 173-180.

Chen, G. and J. Ratcliffe (2015). "A Review of the Development and Application of Generic Multi-Attribute Utility Instruments for Paediatric Populations." PharmacoEconomics **33**(10): 1013-1028.

Chen, S. F. and H. C. Lin (2009). "Dental service utilization and costs before and after introduction of fluoride gel application for preschool children in Taiwan." Health Policy **91**(1): 94-101.

Chestnutt, I. G., S. Hutchings, R. Playle, S. Morgan-Trimmer, D. Fitzsimmons, N. Aawar, L. Angel, S. Derrick, C. Drew, C. Hoddell, K. Hood, I. Humphreys, N. Kirby, T. M. M. Lau, C. Lisles, M. Z. Morgan, S. Murphy, J. Nuttall, K. Onishchenko, C. Phillips, T. Pickles, C. Scoble, J. Townson, B. Withers and B. L. Chadwick (2017). "Seal or Varnish? A randomised controlled trial to determine the relative cost and effectiveness of pit and fissure sealant and fluoride varnish in preventing dental decay." Health Technol Assess **21**(21): 1-256.

Chi, D. L., D. N. van der Goes and J. P. Ney (2014). "Cost-effectiveness of pit-and-fissure sealants on primary molars in Medicaid-enrolled children." American Journal of Public Health **104**(3): 555-561.

Childsmile. (2011). "Incorporating Childsmile into the SDR." Retrieved 22 April, 2020, from http://www.child-smile.org.uk/documents/5475.aspx.

Childsmile. (2019a). "Fluoride varnish application protocol." from http://www.child-smile.org.uk/professionals/childsmile-protocols/fluoridevarnishapp.aspx.

Childsmile. (2019b). "National Standards for Nursery and School Toothbrushing Programmes." Retrieved 15 April, 2020, from http://www.child-smile.org.uk/uploads/documents/5040-National%20standards%20for%20nursery%20and%20school%20toothbrushing%20programmes-August2019-English.pdf.

Childsmile. (2020a). "About Childsmile - Childsmile Core." Retrieved 15 April, 2020, from http://www.child-smile.org.uk/professionals/childsmile-core.aspx.

Childsmile. (2020b). "Childsmile website - About Childsmile." Retrieved 15 April, 2020, from http://www.child-smile.org.uk/professionals/about-childsmile.aspx.

Childsmile Central Evaluation & Research Team (2019). Childsmile National Headline Data. Glasgow, University of Glasgow.

Chiou, C.-F., J. W. Hay, J. F. Wallace, B. S. Bloom, P. J. Neumann, S. D. Sullivan, H.-T. Yu, E. B. Keeler, J. M. Henning and J. J. Ofman (2003). "Development and validation of a grading system for the quality of cost-effectiveness studies." Medical care: 32-44.

Chiou, C. F., M. R. Weaver, M. A. Bell, T. A. Lee and J. W. Krieger (2005). "Development of the multi-attribute Pediatric Asthma Health Outcome Measure (PAHOM)." Int J Qual Health Care **17**(1): 23-30.

Christell, H., S. Birch, K. Horner, C. Lindh and M. Rohlin (2014). "Economic evaluation of diagnostic methods used in dentistry. A systematic review." Journal of Dentistry **42**(11): 1361-1371.

Chu, C., E. Lo and H. Lin (2002). "Effectiveness of silver diamine fluoride and sodium fluoride varnish in arresting dentin caries in Chinese pre-school children." Journal of dental research **81**(11): 767-770.

Claxton, K., S. Martin, M. Soares, N. Rice, E. Spackman, S. Hinde, N. Devlin, P. Smith and M. Sculpher (2015). "Methods for the Estimation of the NICE Cost Effectiveness Threshold." Health Technology Assessment **19**(14).

Coffin, D., J. Craig, M. Arber and J. Glanville (2013). Literature Review of Economic Evaluations on Oral Health Improvement Programmes and Interventions. York, National Institute for Health and Care Excellence (NICE).

Colak, H., C. T. Dülgergil, M. Dalli and M. M. Hamidi (2013). "Early childhood caries update: A review of causes, diagnoses, and treatments." Journal of natural science, biology, and medicine **4**(1): 29-38.

Connolly, P., S. Miller, F. Kee, S. Sloan, A. Gildea, E. McIntosh and J. M. Bland (2018). "A cluster randomised controlled trial and evaluation and cost-effectiveness analysis of the Roots of Empathy schools-based programme for improving social and emotional well-being outcomes among 8-to 9-year-olds in Northern Ireland." Public Health Research.

Conway, D. I., I. Quarrell, D. R. McCall, H. Gilmour, R. Bedi and L. M. Macpherson (2007). "Dental caries in 5-year-old children attending multi-ethnic schools in Greater Glasgow--the impact of ethnic background and levels of deprivation." Community Dent Health **24**(3): 161-165.

Conway, D. I., A. D. McMahon, D. Robertson and L. M. D. Macpherson (2014). Epidemiology of Dental Diseases. Handbook of Epidemiology. W. Ahrens and I. Pigeot. New York, NY, Springer New York**:** 2321-2353.

Cunha, F. and J. Heckman (2007). "The technology of skill formation." American Economic Review **97**(2): 31-47.

Cunha, F. and J. J. Heckman (2010). Investing in our young people, National bureau of economic research.

Cunnion, D. T., A. Spiro, 3rd, J. A. Jones, S. E. Rich, C. P. Papageorgiou, A. Tate, P. Casamassimo, C. Hayes and R. I. Garcia (2010). "Pediatric oral health-related quality of life improvement after treatment of early childhood caries: a prospective multisite study." J Dent Child (Chic) **77**(1): 4-11.

Curtis, L. and A. Burns (2017). Unit Costs of Health and Social Care 2017. University of Kent, Canterbury, Personal Social Services Research Unit.

Dahlquist, L. M., T. G. Power, C. N. Cox and D. J. Fernbach (1994). "Parenting and child distress during cancer procedures: a multidimensional assessment." Child Health Care **23**(3): 149-166.

Davies, G. M., H. V. Worthington, R. P. Ellwood, A. S. Blinkhorn, G. O. Taylor, R. M. Davies and J. Considine (2003). "An assessment of the cost effectiveness of a postal toothpaste programme to prevent caries among five-year-old children in the North West of England." Community Dental Health **20**(4): 207-210.

de Sousa, F. S. d. O., A. P. P. Dos Santos, P. Nadanovsky, P. Hujoel, J. Cunha-Cruz and B. H. de Oliveira (2019). "Fluoride varnish and dental caries in

preschoolers: a systematic review and meta-analysis." Caries Research **53**(5): 502-513.

Designed to Smile. (2020). "Designed to Smile. National child oral health improvement programme in Wales. Website." Retrieved July, 2020, from https://www.designedtosmile.org/welcome-croeso/welcome/.

Devlin, N., R. Norman, J. Ratcliffe, B. Mulhern, K. Dalziel, G. Chen and R. Viney (2020). "Do child QALYs = adult QALYs? Five reasons why they might not." OHE News https://www.ohe.org/news/do-child-qalys-adult-qalys-five-reasons-why-they-might-not Accessed August 2020.

Diaz, C., B. Starfield, N. Holtzman, E. Mellits, J. Hankin, K. Smalky and P. Benson (1986). "Ill health and use of medical care: Community-based assessment of morbidity in children." Medical Care: 848-856.

Dolan, P. (1997). "Modeling valuations for EuroQol health states." Med Care **35**(11): 1095-1108.

Donaldson, C., J. F. Forbes, M. Smalls, F. A. Boddy, K. W. Stephen and D. McCall (1986). "Preventive dentistry in a health centre: effectiveness and cost." Social Science & Medicine **23**(9): 861-868.

Donaldson, C. and G. Mooney (1991). "Needs assessment, priority setting, and contracts for health care: an economic view." BMJ: British Medical Journal **303**(6816): 1529.

Doshi, M. and J. Patel (2017). "Putting the mouth back into the body." Br J Hosp Med (Lond) **78**(5): 244-245.

Dowell, T. B. (1976). "The economics of fluoridation." British Dental Journal **140**(3): 103-106.

Doyle, O., R. E. Tremblay, C. Harmon and J. J. Heckman (2007). "Early childhood intervention: rationale, timing, and efficacy."

Drummond, M., G. Torrance and J. Mason (1993). "Cost-effectiveness league tables: More harm than good?" Social Science & Medicine **37**(1): 33-40.

Drummond, M. (2001). "Introducing economic and quality of life measurements into clinical studies." Annals of Medicine **33**(5): 344-349.

Drummond, M., A. Manca and M. Sculpher (2005a). "Increasing the generalizability of economic evaluations: recommendations for the design, analysis, and reporting of studies." Int J Technol Assess Health Care **21**(2): 165-171.

Drummond, M. F. and T. O. Jefferson (1996). "Guidelines for authors and peer reviewers of economic submissions to the BMJ. The BMJ Economic Evaluation Working Party." BMJ **313**(7052): 275-283.

Drummond, M. F., M. J. Sculpher, G. W. Torrance, B. J. O'Brien and G. L. Stoddart (2005b). Methods for the economic evaluation of health care programmes. Oxford, Oxford University Press.

Drummond, M. F., M. J. Sculpher, G. W. Torrance, B. J. O'Brien and G. L. Stoddart (2005c). Methods for the economic evaluation of health care programmes. Oxford, Oxford University Press.

Drummond, M. F., M. J. Sculpher, K. Claxton, G. L. Stoddart and G. W. Torrance (2015). Methods for the economic evaluation of health care programmes, Oxford University Press.

Drury, T. F., A. M. Horowitz, A. I. Ismail, M. P. Maertens, R. G. Rozier and R. H. Selwitz (1999). "Diagnosing and reporting early childhood caries for research purposes: a report of a workshop sponsored by the National Institute of Dental and Craniofacial Research, the Health Resources and Services Administration, and the Health Care Financing Administration." Journal of public health dentistry **59**(3): 192-197.

Edelstein, B. L. (2006). The dental caries pandemic and disparities problem. BMC Oral Health, Springer.

Edelstein, B. L. (2009). "Solving the problem of early childhood caries: a challenge for us all." Archives of pediatrics & adolescent medicine **163**(7): 667-668.

Edelstein, B. L., G. Hirsch, M. Frosh and J. Kumar (2015). "Reducing early childhood caries in a Medicaid population: a systems model analysis." Journal of the American Dental Association **146**(4): 224-232.

Edwards, H. (2013). BDA Research Findings 8: Dental Care Professionals' Pay – Findings from the Dental Business Trends Survey. London, British Dental Associaton.

Edwards, R., L. Bryning and H. Lloyd-Williams (2016). Transforming Young Lives across Wales: the Economic Argument for Investing in the Early Years. Bangor, Centre for Health Economics and Medicines Evaluation, Bangor University.

Edwards, R. T. and E. McIntosh (2019). Applied health economics for public health practice and research, Oxford University Press.

Eichler, H.-G., S. X. Kong, W. C. Gerth, P. Mavros and B. Jönsson (2004). "Use of Cost-Effectiveness Analysis in Health-Care Resource Allocation Decision-Making: How Are Cost-Effectiveness Thresholds Expected to Emerge?" Value in Health **7**(5): 518-528.

Eisen, M., J. E. Ware Jr, C. A. Donald and R. H. Brook (1979). "Measuring components of children's health status." Medical care: 902-921.

Eiser, C. and R. Morse (2001). "Can parents rate their child's health-related quality of life? Results of a systematic review." Quality of Life Research **10**(4): 347-357.

EuroQol Group (1990). "EuroQol-a new facility for the measurement of health-related quality of life." Health policy **16**(3): 199-208.

EuroQol Group. (2020). "EuroQol Website: EQ-5D-Y (Youth) | About." Retrieved November, 2020, from https://euroqol.org/eq-5d-instruments/eq-5d-y-about/.

Evers, S., M. Goossens, H. de Vet, M. van Tulder and A. Ament (2005). "Criteria list for assessment of methodological quality of economic evaluations: Consensus on Health Economic Criteria." International Journal of Technology Assessment in Health Care **21**(2): 240-245.

Faggion, C. M. and U. Tonmukayakul (2016). Case Study in Dentistry. Umbrella Reviews: Evidence Synthesis with Overviews of Reviews and Meta-Epidemiologic Studies. G. Biondi-Zoccai. Cham, Springer International Publishing**:** 217-234.

Faria, R., M. Gomes, D. Epstein and I. R. White (2014). "A Guide to Handling Missing Data in Cost-Effectiveness Analysis Conducted Within Randomised Controlled Trials." PharmacoEconomics **32**(12): 1157-1170.

FDI. (2015). "Policy Statements: Oral Health and Quality of Life." Retrieved 15 April, 2020, from https://www.fdiworlddental.org/resources/policy-statements-and-resolutions/oral-health-and-quality-of-life.

FDI World Dental Federation (2016). Caries Prevention Partnership. Making prevention a priority. Advocacy Toolkit. Genève, FDI World Dental Federation.

Feeny, D., W. Furlong, G. W. Torrance, C. H. Goldsmith, Z. Zhu, S. DePauw, M. Denton and M. Boyle (2002). "Multiattribute and single-attribute utility functions for the health utilities index mark 3 system." Med Care **40**(2): 113-128.

Fejerskov, O. (1997). "Concepts of dental caries and their consequences for understanding the disease." Community Dent Oral Epidemiol **25**(1): 5-12.

Fejerskov, O., J. A. Cury, L. M. Tenuta and V. C. C. Marinho (2015). Fluorides in caries control. Dental Caries The Disease and Its Clinical Management. Third Edition. O. Fejerskov, B. Nyvad and E. Kidd. West Sussex, UK, John Wiley and Sons Ltd.

Fekkes, M., N. C. M. Theunissen, E. Brugman, S. Veen, E. G. H. Verrips, H. M. Koopman, T. Vogels, J. M. Wit and S. P. Verloove-Vanhorick (2000). "Development and psychometric evaluation of the TAPQOL: A health-related quality of life instrument for 1–5-year-old children." Quality of Life Research **9**(8): 961-972.

Ferguson, B. (2018). "Cost savings and the economic case for investing in public health." Public health matters https://publichealthmatters.blog.gov.uk/2018/04/09/cost-savings-and-the-economic-case-for-investing-in-public-health/ Accessed September 2020.

Fidler, P. E. (1977). "A comparison of treatment patterns and costs for a fluoride and non-fluoride community." Community Health **9**(2): 103-113.

Filstrup, S. L., D. Briskie, M. da Fonseca, L. Lawrence, A. Wandera and M. R. Inglehart (2003). "Early childhood caries and quality of life: child and parent perspectives." Pediatr Dent **25**(5): 431-440.

Finch, D., A. Briggs and C. Tallack. (2020). "Improving health by tackling market failure." Retrieved September, 2020, from https://www.health.org.uk/publications/long-reads/improving-health-by-tackling-market-failure.

Foster Page, L. A., W. M. Thomson, Z. Marshman and K. J. Stevens (2014). "The potential of the Child Health Utility 9D Index as an outcome measure for child dental health." BMC Oral Health **14**(1): 90.

Foster Page, L. A., D. M. Beckett, C. M. Cameron and W. M. Thomson (2015). "Can the Child Health Utility 9D measure be useful in oral health research?" International Journal of Paediatric Dentistry **25**(5): 349-357.

Frederix, G. W. J. (2019). "Check Your Checklist: The Danger of Over- and Underestimating the Quality of Economic Evaluations." Pharmacoecon Open.

Frencken, J. E., P. Sharma, L. Stenhouse, D. Green, D. Laverty and T. Dietrich (2017). "Global epidemiology of dental caries and severe periodontitis – a comprehensive review." Journal of Clinical Periodontology **44**(S18): S94-S105.

Frew, E. J., M. Pallan, E. Lancashire, K. Hemming, P. Adab and W. S. c.-i. on behalf of the (2015). "Is utility-based quality of life associated with overweight in children? Evidence from the UK WAVES randomised controlled study." BMC Pediatrics **15**(1): 211.

Fyffe, H. E., C. Deery, Z. Nugent, N. M. Nuttall and N. B. Pitts (1999). "The reliability of two methods of utility assessment in dentistry." Community dental health **16**(2): 72-79.

Gao, X.-L., C. McGrath and H.-C. Lin (2011). "Oral health status of rural–urban migrant children in South China." International Journal of Paediatric Dentistry **21**(1): 58-67.

Gargiullo, P. M., R. B. Rothenberg and H. G. Wilson (1995). "Confidence intervals, hypothesis tests, and sample sizes for the prevented fraction in cross-sectional studies." Statistics in Medicine **14**(1): 51-72.

Geisler, B. P., Y. D. Ji and Z. S. Peacock (2017). "Value in Oral and Maxillofacial Surgery: A Systematic Review of Economic Analyses." Journal of Oral and Maxillofacial Surgery **75**(11): 2287-2303.

Genderson, M. W., M. W. Genderson, L. Sischo, K. Markowitz, D. Fine and H. L. Broder (2013). "An Overview of Children's Oral Health-Related Quality of Life Assessment: From Scale Development to Measuring Outcomes." Caries Research **47(suppl 1)**(Suppl. 1): 13-21.

Germain, N., S. Aballéa and M. Toumi (2019). "Measuring health-related quality of life in young children: how far have we come?" Journal of Market Access & Health Policy **7**(1): 1618661.

Gilchrist, F., H. Rodd, C. Deery and Z. Marshman (2014). "Assessment of the quality of measures of child oral health-related quality of life." BMC Oral Health **14**(1): 40.

Gilchrist, F., H. D. Rodd, C. Deery and Z. Marshman (2018). "Development and evaluation of CARIES-QC: a caries-specific measure of quality of life for children." BMC Oral Health **18**(1): 202.

Gisselsson, H., D. Birkhed and A. L. Bjorn (1994). "Effect of a 3-year professional flossing program with chlorhexidine gel on approximal caries and cost of treatment in preschool children." Caries Research **28**(5): 394-399.

Glanville, J., K. Fleetwood, A. Yellowlees, D. Kaunelis and S. Mensinkai (2009). Development and Testing of Search Filters to Identify Economic Evaluations in MEDLINE and EMBASE. Ottawa, Canadian Agency for Drugs and Technologies in Health.

Glick, H. A., J. A. Doshi, S. S. Sonnad and D. Polsky (2014). Economic evaluation in clinical trials, OUP Oxford.

Godson, J., J. Csikar and S. White (2018). "Oral health of children in England: a call to action!" Archives of Disease in Childhood **103**(1): 5.

Gold, M. R., J. E. Siegel, L. B. Russell and M. C. Weinstein (1996). Cost-effectiveness in health and medicine. New York, Oxford University Press.

Gold, M. R., D. Stevenson and D. G. Fryback (2002). "HALYS and QALYS and DALYS, Oh My: similarities and differences in summary measures of population Health." Annu Rev Public Health **23**: 115-134.

Goodacre, S. and C. McCabe (2002). "An introduction to economic evaluation." Emergency Medicine Journal **19**(3): 198.

Goossens, M. E., S. M. Evers, J. W. Vlaeyen, M. P. R. v. Mölken and S. M. van der Linden (1999). "Principles of economic evaluation for interventions of chronic musculoskeletal pain." European Journal of Pain **3**(4): 343-353.

Graf von der Schulenburg, J. M., W. Greiner, F. Jost, N. Klusen, M. Kubin, R. Leidl, T. Mittendorf, H. Rebscher, O. Schoeffski, C. Vauth, T. Volmer, S. Wahler, J. Wasem, C. Weber and G. the Hanover Consensus (2008). "German Recommendations on Health Economic Evaluation: Third and Updated Version of the Hanover Consensus." Value in Health **11**(4): 539-544.

Graham, J. W., A. E. Olchowski and T. D. Gilreath (2007). "How Many Imputations are Really Needed? Some Practical Clarifications of Multiple Imputation Theory." Prevention Science **8**(3): 206-213.

Grange, A., H. Bekker, J. Noyes and P. Langley (2007). "Adequacy of health-related quality of life measures in children under 5 years old: systematic review." Journal of Advanced Nursing **59**(3): 197-220.

Griebsch, I., J. Coast and J. Brown (2005). "Quality-adjusted life-years lack quality in pediatric care: a critical review of published cost-utility studies in child health." Pediatrics **115**(5): e600-614.

Griffin, S. (2020). "Covid-19: UK's response has so far cost "unprecedented" £124.3bn." BMJ **369**: m2057.

Grodzka, K., L. Augustyniak, J. Budny, K. Czarnocka, J. Janicha, K. Mlosek, B. Moszczeńska, M. Szpringer, M. Wacińska and L. Petersson (1982). "Caries increment in primary teeth after application of Duraphat® fluoride varnish." Community dentistry and oral epidemiology **10**(2): 55-59.

Haber, J., E. Hartnett, K. Allen, D. Hallas, C. Dorsen, J. Lange-Kessler, M. Lloyd, E. Thomas and D. Wholihan (2015). "Putting the Mouth Back in the Head: HEENT to HEENOT." American Journal of Public Health **105**(3): 437-441.

Hale, J., C. J. Phillips and T. Jewell (2012). "Making the economic case for prevention – a view from Wales." BMC Public Health **12**(1): 460.

Hall-Scullin, E., H. Whitehead, K. Milsom, M. Tickle, T.-L. Su and T. Walsh (2017). "Longitudinal Study of Caries Development from Childhood to Adolescence." Journal of Dental Research **96**(7): 762-767.

Hamelmann, C., F. Turatto, V. Then and M. Dyakova (2017). "Social return on investment: Accounting for value in the context of implementing Health 2020 and the 2030 Agenda for Sustainable Development." Copenhagen: WHO Regional Office for Europe.

Harris, C. M., R. Welbury and A. M. Cairns (2013). "The Scottish dental practitioner's role in managing child abuse and neglect." British Dental Journal **214**(9): E24-E24.

Harris, J. C., R. C. Balmer and P. D. Sidebotham (2009). "British Society of Paediatric Dentistry: a policy document on dental neglect in children." International Journal of Paediatric Dentistry **28**(5): e14-e21.

Harstick-Koll, S., A. Kuschel, H. Bertram, S. Naumann, K. Hahlweg, C. Hautmann and M. Döpfner (2009). "Erfassung der Lebensqualität von Vorschulkindern mit dem Kiddy-KINDLR." Zeitschrift für Gesundheitspsychologie **17**(2): 82-93.

Hassan, A. H., M. H. Hassan and A. I. Linjawi (2014). "Association of orthodontic treatment needs and oral health-related quality of life in Saudi children seeking orthodontic treatment." Patient preference and adherence **8**: 1571-1579.

Hawkins, R., J. Noble, D. Locker, D. Wiebe, H. Murray, P. Wiebe, C. Frosina and M. Clarke (2004). "A comparison of the costs and patient acceptability of professionally applied topical fluoride foam and varnish." Journal of Public Health Dentistry **64**(2): 106-110.

Heckman, J. J. and D. V. Masterov (2007). "The productivity argument for investing in young children." Applied Economic Perspectives and Policy **29**(3): 446-493.

Heckman, J. J. (2008). "Schools, skills, and synapses." Economic inquiry **46**(3): 289-324.

Heckman, J. J. (2011). "Effective child development strategies." The pre-K debates: Current controversies and issues: 2-8.

Herdman, M., C. Gudex, A. Lloyd, M. Janssen, P. Kind, D. Parkin, G. Bonsel and X. Badia (2011). "Development and preliminary testing of the new five-level version of EQ-5D (EQ-5D-5L)." Qual Life Res **20**(10): 1727-1736.

Hettiarachchi, R. M., S. Kularatna, M. J. Downes, J. Byrnes, J. Kroon, R. Lalloo, N. W. Johnson and P. A. Scuffham (2018). "The cost-effectiveness of oral health interventions: A systematic review of cost-utility analyses." Community dentistry and oral epidemiology **46**(2): 118-124.

Hettiarachchi, R. M., S. Kularatna, J. Byrnes and P. A. Scuffham (2019). "Pediatric Quality of Life Instruments in Oral Health Research: A Systematic Review." Value in Health **22**(1): 129-135.

Higgins, J. and S. Green (2011). Cochrane handbook for systematic reviews of interventions. Version 5.1.0, The Cochrane Collaboration.

Hill, H., D. Rowen, B. Pennington, R. Wong and A. Wailoo (2019). A review of the methods used to estimate and model utility values in nice technology appraisals for paediatric populations Sheffield, UK, Decision Support Unit, ScHARR, University of Sheffield.

Hirsch, G. B., B. L. Edelstein, M. Frosh and T. Anselmo (2012). "A simulation model for designing effective interventions in early childhood caries." Preventing Chronic Disease **9**: E66.

HM Revenue and Customs. (2012). "Guidance: Travel - mileage and fuel rates and allowances." Retrieved 16th Dec, 2019, from https://www.gov.uk/government/publications/rates-and-allowances-travel-mileage-and-fuel-allowances/travel-mileage-and-fuel-rates-and-allowances.

HM Treasury (2018). The Green Book. Central Government Guidance On Appraisal And Evaluation. London, HM Treasury.

Hughes, D., J. Charles, D. Dawoud, R. T. Edwards, E. Holmes, C. Jones, P. Parham, C. Plumpton, C. Ridyard and H. Lloyd-Williams (2016). "Conducting economic evaluations alongside randomised trials: current methodological issues and novel approaches." Pharmacoeconomics **34**(5): 447-461.

Hullmann, S. E., J. L. Ryan, R. R. Ramsey, J. M. Chaney and L. L. Mullins (2011). "Measures of general pediatric quality of life: Child Health Questionnaire (CHQ), DISABKIDS Chronic Generic Measure (DCGM), KINDL-R, Pediatric Quality of Life Inventory (PedsQL) 4.0 Generic Core Scales, and Quality of My Life Questionnaire (QoML)." Arthritis Care & Research **63**(S11): S420-S430.

Hunter, R. and J. Shearer. (2019). "Cost-consequences analysis - an underused method of economic evaluation." from https://www.rds-london.nihr.ac.uk/resources/health-economics/cost-consequences-analysis-an-underused-method/.

Huntington, N. L., D. Spetter, J. A. Jones, S. E. Rich, R. I. Garcia and A. Spiro Iii (2011). "Development and validation of a measure of pediatric oral health-related quality of life: the POQL." Journal of Public Health Dentistry **71**(3): 185-193.

Husereau, D., M. Drummond, S. Petrou, C. Carswell, D. Moher, D. Greenberg, F. Augustovski, A. H. Briggs, J. Mauskopf and E. Loder (2013a). "Consolidated Health Economic Evaluation Reporting Standards (CHEERS)—Explanation and Elaboration: A Report of the ISPOR Health Economic Evaluation Publication Guidelines Good Reporting Practices Task Force." Value in Health **16**(2): 231-250.

Husereau, D., M. Drummond, S. Petrou, C. Carswell, D. Moher, D. Greenberg, F. Augustovski, A. H. Briggs, J. Mauskopf and E. Loder (2013b). "Consolidated Health Economic Evaluation Reporting Standards (CHEERS) statement." BMC Medicine **11**(1): 80.

ICOHIRP (2015). Social inequalities in oral health: from evidence to action. R. G. Watt, S. Listl, M. Peres and A. Heilmann. London, International Centre for Oral Health Inequalities Research & Policy.

Innes, N. P. T. and M. D. Robertson (2018). "Recent advances in the management of childhood dental caries." Archives of Disease in Childhood **103**(4): 311.

IntHout, J., J. P. A. Ioannidis, M. M. Rovers and J. J. Goeman (2016). "Plea for routinely presenting prediction intervals in meta-analysis." BMJ Open **6**(7): e010247.

ISD Scotland (2014). Dental Statistics – NHS Treatment and Fees. Statistics up to financial year 2013/14.

Ismail, A. I. (2003). "Determinants of health in children and the problem of early childhood caries." Pediatr Dent **25**(4): 328-333.

Ismail, A. I. (2004). "Visual and visuo-tactile detection of dental caries." J Dent Res **83 Spec No C**: C56-66.

Jankauskiene, B. and J. Narbutaite (2010). "Changes in oral health-related quality of life among children following dental treatment under general anaesthesia. A systematic review." Stomatologija **12**(2): 60-64.

Johannesson, M. and B. Jönsson (1991). "Economic evaluation in health care: Is there a role for cost-benefit analysis?" Health Policy **17**(1): 1-23.

Johannesson, M., B. Jonsson and G. Karlsson (1996). "Outcome measurement in economic evaluation." Health Econ **5**(4): 279-296.

Jokela, J. and K. Pienihakkinen (2003). "Economic evaluation of a risk-based caries prevention program in preschool children." Acta Odontologica Scandinavica **61**(2): 110-114.

Jokovic, A., D. Locker, M. Stephens, D. Kenny, B. Tompson and G. Guyatt (2003). "Measuring parental perceptions of child oral health-related quality of life." Journal of public health dentistry **63**(2): 67-72.

Jong, A. and G. S. Leske (1968). "Utilization and cost of dental services for preschool children in Boston's Head-Start program." Journal of Public Health Dentistry **28**(2): 126-134.

Juniper, E. F., P. M. O'Byrne, G. H. Guyatt, P. J. Ferrie and D. R. King (1999). "Development and validation of a questionnaire to measure asthma control." Eur Respir J **14**(4): 902-907.

Kaakko, T., E. Skaret, T. Getz, P. Hujoel, D. Grembowski, C. S. Moore and P. Milgrom (2002). "An ABCD program to increase access to dental care for children enrolled in Medicaid in a rural county." Journal of Public Health Dentistry **62**(1): 45-50.

Kallestal, C., A. Norlund, B. Soder, G. Nordenram, H. Dahlgren, L. G. Petersson, F. Lagerlof, S. Axelsson, P. Lingstrom, I. Mejare, A. K. Holm and S. Twetman (2003). "Economic evaluation of dental caries prevention: a systematic review." Acta Odontologica Scandinavica **61**(6): 341-346.

Karimi, M. and J. Brazier (2016). "Health, Health-Related Quality of Life, and Quality of Life: What is the Difference?" PharmacoEconomics **34**(7): 645-649.

Kassebaum, N. J., A. G. C. Smith, E. Bernabé, T. D. Fleming, A. E. Reynolds, T. Vos, C. J. L. Murray and W. Marcenes (2017). "Global, Regional, and National Prevalence, Incidence, and Disability-Adjusted Life Years for Oral Conditions for 195 Countries, 1990–2015: A Systematic Analysis for the Global Burden of Diseases, Injuries, and Risk Factors." Journal of Dental Research **96**(4): 380-387.

Keren, R., S. Pati and C. Feudtner (2004). "The Generation Gap." PharmacoEconomics **22**(2): 71-81.

Kickbusch, I., L. Allen and C. Franz (2016). "The commercial determinants of health." The Lancet Global Health **4**(12): e895-e896.

Kidd, E. and O. Fejerskov (2016). Essentials of Dental Caries. Oxford, Oxford University Press.

Kidd, J. (2019). Developing a population data linkage cohort to investigate the impact on child oral health outcomes following the roll-out of the Childsmile programme in Scotland. PhD, University of Glasgow.

Kind, P., K. Klose, N. Gusi, P. R. Olivares and W. Greiner (2015). "Can adult weights be used to value child health states? Testing the influence of perspective in valuing EQ-5D-Y." Quality of Life Research **24**(10): 2519-2539.

King, S., H. Schwellnus, D. Russell, L. Shapiro and A. O. (2005). "Assessing Quality of Life of Children and Youth with Disabilities: A Review of Available Measures." Retrieved May, 2014, from http://www.canchild.ca/en/canchildresources/assessingqualityoflife.asp.

Kirthiga, M., M. Murugan, A. Saikia and R. Kirubakaran (2019). "Risk factors for early childhood caries: a systematic review and meta-analysis of case control and cohort studies." Pediatric dentistry **41**(2): 95-112.

Klaassen, M. A., J. S. Veerkamp and J. Hoogstraten (2008). "Dental treatment under general anaesthesia: the short-term change in young children's oral-health-related quality of life." Eur Arch Paediatr Dent **9**(3): 130-137.

Klaassen, M. A., J. S. Veerkamp and J. Hoogstraten (2009). "Young children's Oral Health-Related Quality of Life and dental fear after treatment under general anaesthesia: a randomized controlled trial." Eur J Oral Sci **117**(3): 273-278.

Klarenbach, S. W., M. Tonelli, B. Chui and B. J. Manns (2014). "Economic evaluation of dialysis therapies." Nat Rev Nephrol **10**(11): 644-652.

Klassen, A. F., J. M. Landgraf, S. K. Lee, M. Barer, P. Raina, H. W. P. Chan, D. Matthew and D. Brabyn (2003). "Health related quality of life in 3 and 4 year old children and their parents: preliminary findings about a new questionnaire." Health and Quality of Life Outcomes **1**(1): 81.

Knapp, R., Z. Marshman and H. Rodd (2017). "Treatment of dental caries under general anaesthetic in children." BDJ Team **4**(7): 17116.

Knapp, R., Z. Marshman, H. Rodd, F. Gilchrist and H. Zaitoun (2018). Impact on children of dental caries and treatment under GA. IADR Abstract Archives, International Association for Dental Research (IADR).

Knapp, R. (2019). The impact of dental caries and its treatment under general anaesthetic on the everyday lives of children and their families. PhD, University of Sheffield.

Kobelt, G. (2013). Health Economics: An Introduction to Economic Evaluation. Third Edition. London, Office of Health Economics.

Koh, R., M. Pukallus, S. Kularatna, L. G. Gordon, A. G. Barnett, L. J. Walsh and W. K. Seow (2015). "Relative cost-effectiveness of home visits and telephone contacts in preventing early childhood caries." Community Dentistry & Oral Epidemiology **43**(6): 560-568.

Kowash, M. B., K. J. Toumba and M. E. Curzon (2006). "Cost-effectiveness of a long-term dental health education program for the prevention of early childhood caries." European Archives of Paediatric Dentistry: Official Journal of the European Academy of Paediatric Dentistry **7**(3): 130-135.

Kranz, A. M., R. G. Rozier, J. S. Preisser, S. C. Stearns, M. Weinberger and J. Y. Lee (2014). "Preventive Services by Medical and Dental Providers and Treatment Outcomes." Journal of Dental Research **93**(7): 633-638.

Kromm, S., J. Bethell, F. Kraglund, S. Edwards, A. Laporte, P. Coyte and W. Ungar (2012). "Characteristics and quality of pediatric cost-utility analyses." Quality of Life Research **21**(8): 1315-1325.

Ladewig, N. M., L. B. Camargo, T. K. Tedesco, I. Floriano, T. Gimenez, J. C. P. Imparato, F. M. Mendes, M. M. Braga and D. P. Raggio (2018). "Management of dental caries among children: a look at the cost-effectiveness." Expert Rev Pharmacoecon Outcomes Res **18**(2): 127-134.

Lafond, S., A. Charlesworth and A. Roberts (2016). A perfect storm: an impossible climate for NHS providers' finances? (An analysis of NHS finances and factors associated with financial performance). London, The Health Foundation.

Langer, A. (2012). "A framework for assessing Health Economic Evaluation (HEE) quality appraisal instruments." BMC Health Services Research **12**(1): 253.

Leal, S. C., E. M. Bronkhorst, M. Fan and J. E. Frencken (2012). "Untreated Cavitated Dentine Lesions: Impact on Children's Quality of Life." Caries Research **46**(2): 102-106.

Leal, S. C., E. M. Bronkhorst, M. Fan and J. E. Frencken (2013). "Effect of different protocols for treating cavities in primary molars on the quality of life of children in Brazil – 1 year follow-up." International Dental Journal **63**(6): 329-335.

Lee, G. H. M., C. McGrath, C. K. Y. Yiu and N. M. King (2010). "A comparison of a generic and oral health–specific measure in assessing the impact of early childhood caries on quality of life." Community Dentistry and Oral Epidemiology **38**(4): 333-339.

Lee, G. H. M., C. McGrath, C. K. Y. Yiu and N. M. King (2011). "Sensitivity and responsiveness of the Chinese ECOHIS to dental treatment under general anaesthesia." Community Dentistry and Oral Epidemiology **39**(4): 372-377.

Levin, K. A., C. A. Davies, G. V. A. Douglas and N. B. Pitts (2010). "Urban-rural differences in dental caries of 5-year old children in Scotland." Social Science & Medicine **71**(11): 2020-2027.

Lewis, D. W., A. M. Hunt, K. Kawall and R. E. Feasby (1972). "Initial dental care time, cost and treatment requirements under changing exposure to fluoride during tooth development." Journal of the Canadian Dental Association **38**(4): 140-144.

Lewis, D. W., S. C. Magid and M. E. Jarrett (1977). "The Waterloo preschool children's denticare study." Dental Journal - Journal Dentaire (Journal of the Canadian Dental Association) **43**(1): 27-34.

Li, J., S. Parrott, M. Sweeting, A. Farmer, J. Ross, C. Dack, K. Pal, L. Yardley, M. Barnard, M. Hudda, G. Alkhaldi and E. Murray (2018). "Cost-Effectiveness of Facilitated Access to a Self-Management Website, Compared to Usual Care, for Patients With Type 2 Diabetes (HeLP-Diabetes): Randomized Controlled Trial." J Med Internet Res **20**(6): e201.

Li, S., S. Malkinson, J. Veronneau and P. J. Allison (2008a). "Testing responsiveness to change for the early childhood oral health impact scale (ECOHIS)." Community Dentistry and Oral Epidemiology **36**(6): 542-548.

Li, S., J. Veronneau and P. Allison (2008b). "Validation of a French language version of the Early Childhood Oral Health Impact Scale (ECOHIS)." Health and Quality of Life Outcomes **6**(1): 9.

Li, Y. and W. Wang (2002). "Predicting caries in permanent teeth from caries in primary teeth: an eight-year cohort study." J Dent Res **81**(8): 561-566.

Liberati, A., D. G. Altman, J. Tetzlaff, C. Mulrow, P. C. Gøtzsche, J. P. A. Ioannidis, M. Clarke, P. J. Devereaux, J. Kleijnen and D. Moher (2009). "The

PRISMA statement for reporting systematic reviews and meta-analyses of studies that evaluate healthcare interventions: explanation and elaboration." BMJ **339**.

Listl, S., J. I. Grytten and S. Birch (2019). "What is health economics?" Community Dent Health **36**(4): 262-274.

Little, R. J. and D. B. Rubin (2019). Statistical analysis with missing data, John Wiley & Sons.

Locker, D., A. Jokovic, M. Stephens, D. Kenny, B. Tompson and G. Guyatt (2002). "Family impact of child oral and oro-facial conditions." Community dentistry and oral epidemiology **30**(6): 438-448.

Locker, D. and F. Allen (2007). "What do measures of 'oral health-related quality of life' measure?" Community Dentistry and Oral Epidemiology **35**(6): 401-411.

Lord, J., L. Longworth, J. Singh, O. Onyimadu, J. Fricke, S. Bayliss and C. Meads (2015). "Oral health guidance – Economic analysis of oral health promotion approaches for dental teams." United Kingdom: Birmingham and Brunel Consortium External Assessment Centre.

Machiulskiene, V., G. Campus, J. C. Carvalho, I. Dige, K. R. Ekstrand, A. Jablonski-Momeni, M. Maltz, D. J. Manton, S. Martignon, E. A. Martinez-Mier, N. B. Pitts, A. G. Schulte, C. H. Splieth, L. M. A. Tenuta, A. Ferreira Zandona and B. Nyvad (2020). "Terminology of Dental Caries and Dental Caries Management: Consensus Report of a Workshop Organized by ORCA and Cariology Research Group of IADR." Caries Res **54**(1): 7-14.

MacNeil Vroomen, J., I. Eekhout, M. G. Dijkgraaf, H. van Hout, S. E. de Rooij, M. W. Heymans and J. E. Bosmans (2016). "Multiple imputation strategies for zero-inflated cost data in economic evaluations: which method works best?" The European Journal of Health Economics **17**(8): 939-950.

Macpherson, L. M., G. E. Ball, L. Brewster, B. Duane, C. L. Hodges, W. Wright, W. Gnich, J. Rodgers, D. R. McCall, S. Turner and D. I. Conway (2010). "Childsmile: the national child oral health improvement programme in Scotland. Part 1: Establishment and development." Br Dent J **209**(2): 73-78.

Macpherson, L. M., Y. Anopa, D. I. Conway and A. D. McMahon (2013). "National supervised toothbrushing program and dental decay in Scotland." J Dent Res **92**(2): 109-113.

Macpherson, L. M., G. E. Ball, P. King, K. Chalmers and W. Gnich (2015). "Childsmile: the child oral health improvement programme in Scotland." Prim Dent J **4**(4): 33-37.

Macpherson, L. M., J. Rodgers and D. I. Conway (2019a). "Childsmile after 10 years part 1: background, theory and principles." Dental Update **46**(2): 113-116.

Macpherson, L. M., J. Rodgers and D. I. Conway (2019b). "Childsmile after 10 years part 2: programme development, implementation and evaluation." Dental Update **46**(3): 238-246.

Mahase, E. (2020). "Covid-19: Charity cuts could put the NHS under even more pressure." BMJ **370**: m3261.

Manca, A. and S. Palmer (2005). "Handling missing data in patient-level cost-effectiveness analysis alongside randomised clinical trials." Applied Health Economics and Health Policy **4**(2): 65-75.

Marcenes, W., N. J. Kassebaum, E. Bernabé, A. Flaxman, M. Naghavi, A. Lopez and C. J. L. Murray (2013). "Global Burden of Oral Conditions in 1990-2010:A Systematic Analysis." Journal of Dental Research **92**(7): 592-597.

Marinho, V. C. C., J. P. T. Higgins, S. Logan and A. Sheiham (2002). "Fluoride varnishes for preventing dental caries in children and adolescents." Cochrane Database of Systematic Reviews(1).

Marinho, V. C. C., H. V. Worthington, T. Walsh and J. E. Clarkson (2013). "Fluoride varnishes for preventing dental caries in children and adolescents." Cochrane Database of Systematic Reviews(7).

Marinho, V. C. C., H. V. Worthington, T. Walsh and L. Y. Chong (2015). "Fluoride gels for preventing dental caries in children and adolescents." Cochrane Database of Systematic Reviews(6).

Marinho, V. C. C., L. Y. Chong, H. V. Worthington and T. Walsh (2016). "Fluoride mouthrinses for preventing dental caries in children and adolescents." Cochrane Database of Systematic Reviews(7).

Marino, R., M. Morgan, A. Weitz and A. Villa (2007). "The cost-effectiveness of adding fluorides to milk-products distributed by the National Food Supplement Programme (PNAC) in rural areas of Chile." Community Dental Health **24**(2): 75-81.

Marino, R. J., A. R. Khan and M. Morgan (2013). "Systematic review of publications on economic evaluations of caries prevention programs." Caries Research **47**(4): 265-272.

Marmot Review (2010). Fair society, healthy lives: strategic review of health inequalities in England post 2010. The Marmot Review. London, Institute of Health Equity.

Marshman, Z. and P. G. Robinson (2007). "Child and Adolescent Oral Health-Related Quality of Life." Seminars in Orthodontics **13**(2): 88-95.

Marshman, Z., E. Gupta, S. R. Baker, P. G. Robinson, J. Owens, H. D. Rodd, P. E. Benson and B. Gibson (2015). "Seen and heard: towards child participation in dental research." International Journal of Paediatric Dentistry **25**(5): 375-382.

Martins-Júnior, P. A., J. Ramos-Jorge, S. M. Paiva, L. S. Marques and M. L. Ramos-Jorge (2012). "Validations of the Brazilian version of the Early Childhood Oral Health Impact Scale (ECOHIS)." Cadernos de Saúde Pública **28**: 367-374.

Masters, R., E. Anwar, B. Collins, R. Cookson and S. Capewell (2017). "Return on investment of public health interventions: a systematic review." Journal of Epidemiology and Community Health **71**(8): 827.

Mathur, V. P., J. K. Dhillon, A. Logani and R. Agarwal (2014). "Development and validation of oral health-related early childhood quality of life tool for North Indian preschool children." Indian Journal of Dental Research **25**(5): 559.

Matthews, J. N., D. G. Altman, M. J. Campbell and P. Royston (1990). "Analysis of serial measurements in medical research." British Medical Journal **300**(6719): 230-235.

Matza, L. S., A. R. Swensen, E. M. Flood, K. Secnik and N. K. Leidy (2004). "Assessment of Health-Related Quality of Life in Children: A Review of Conceptual, Methodological, and Regulatory Issues." Value in Health **7**(1): 79-92.

Matza, L. S., D. L. Patrick, A. W. Riley, J. J. Alexander, L. Rajmil, A. M. Pleil and M. Bullinger (2013). "Pediatric patient-reported outcome instruments for research to support medical product labeling: report of the ISPOR PRO good research practices for the assessment of children and adolescents task force." Value in Health **16**(4): 461-479.

Mauskopf, J., F. Rutten and W. Schonfeld (2003). "Cost-effectiveness league tables." PharmacoEconomics **21**(14): 991-1000.

McCabe, C., K. Stevens, J. Roberts and J. Brazier (2005). "Health state values for the HUI 2 descriptive system: results from a UK survey." Health economics **14**(3): 231-244.

McIntosh, E. and R. Luengo-Fernandez (2006). "Economic evaluation. Part 2: frameworks for combining costs and benefits in health care." BMJ Sexual & Reproductive Health **32**(3): 176.

McIntosh, E., P. Clarke, E. Frew and J. Louviere (2010). Applied methods of cost-benefit analysis in health care, Oxford University Press.

McKee, M. and D. Stuckler (2018). "Revisiting the corporate and commercial determinants of health." American journal of public health **108**(9): 1167-1170.

McMahon, A. D., Y. Blair, D. R. McCall and L. M. D. Macpherson (2010). "The dental health of three-year-old children in Greater Glasgow, Scotland." British Dental Journal **209**(4): E5-E5.

McMahon, A. D., W. Wright, Y. Anopa, E. McIntosh, S. Turner, D. I. Conway and L. M. D. Macpherson (2020). "Fluoride Varnish in Nursery Schools: A Randomised Controlled Trial – Protecting Teeth @3." Caries Research.

Mejare, I. A., G. Klingberg, F. K. Mowafi, C. Stecksen-Blicks, S. H. Twetman and S. H. Tranaeus (2015). "A systematic map of systematic reviews in pediatric dentistry--what do we really know?" PLoS One **10**(2): e0117537.

Merrett, M. C. W., S. Goold, C. M. Jones, D. R. Mccall, L. M. D. Macpherson, Z. J. Nugent and G. V. A. Topping (2006). National Dental Inspection Programme of

Scotland Report of the 2006 Survey of P1 Children, Scottish Dental Epidemiological Co-ordinating Committee.

Meyer, F. and J. Enax (2018). "Early Childhood Caries: Epidemiology, Aetiology, and Prevention." International Journal of Dentistry **2018**: 1415873.

Miller, P. (2009). An Introduction to Health Economic Evaluation, The NIHR Research Design Service for the East Midlands / Yorkshire & the Humber.

Milsom, K., A. Blinkhorn and M. Tickle (2008). "The incidence of dental caries in the primary molar teeth of young children receiving National Health Service funded dental care in practices in the North West of England." British Dental Journal **205**(7): E14-E14.

Mitton, C., S. Patten, H. Waldner and C. Donaldson (2003). "Priority setting in health authorities: a novel approach to a historical activity." Social Science & Medicine **57**(9): 1653-1663.

Mitton, C. and C. Donaldson (2009). Priority setting toolkit: guide to the use of economics in healthcare decision making, John Wiley & Sons.

Mooney, G. H. and A. McGuire (1988). "Medical ethics and economics in health care."

Mooney, G. H. (1992). Economics, medicine and health care. London, Harvester Wheatsheaf.

Moran, J. L., P. J. Solomon, A. R. Peisach and J. Martin (2007). "New models for old questions: generalized linear models for cost prediction." J Eval Clin Pract **13**(3): 381-389.

Morgan, M., R. Mariño, C. Wright, D. Bailey and M. Hopcraft (2012). "Economic evaluation of preventive dental programs: what can they tell us?" Community Dentistry and Oral Epidemiology **40**(s2): 117-121.

Munz, S. M., S. P. Edwards and M. R. Inglehart (2011). "Oral health-related quality of life, and satisfaction with treatment and treatment outcomes of adolescents/young adults with cleft lip/palate: an exploration." International Journal of Oral and Maxillofacial Surgery **40**(8): 790-796.

Murray, J., C. Vernazza and R. Holmes (2015). "Forty years of national surveys: An overview of children's dental health from 1973-2013." British Dental Journal **219**(6): 281-285.

Mwachofi, A. and A. F. Al-Assaf (2011). "Health care market deviations from the ideal market." Sultan Qaboos University Medical Journal **11**(3): 328.

NDIP (2014). National Dental Inspection Programme (NDIP) 2014. Report of the 2014 Detailed Inspection Programme of Primary 1 Children and the Basic Inspection of Primary 1 and Primary 7 children.

NDIP (2018). National Dental Inspection Programme (NDIP) 2018. Report of the 2018 Detailed Inspection Programme of Primary 1 Children and the Basic Inspection of Primary 1 and Primary 7 children. .

NDIP (2020). National Dental Inspection Programme (NDIP) 2020. Report of the 2020 Detailed Inspection Programme of Primary 1 Children and the Basic Inspection of Primary 1 and Primary 7 children. .

Neidell, M., B. Shearer and I. B. Lamster (2016). "Cost-Effectiveness Analysis of Dental Sealants versus Fluoride Varnish in a School-Based Setting." Caries Research **50(suppl 1)**(Suppl. 1): 78-82.

Ney, J. P., D. N. van der Goes and D. L. Chi (2014). "Economic modeling of sealing primary molars using a "value of information" approach." Journal of dental research **93**(9): 876-881.

NHS Digital (2018). Dental Earnings and Expenses Estimates 2016/17.

NHS Improvement. (2017a). "2016/17 NHS reference costs and guidance." Retrieved July, 2019, from https://improvement.nhs.uk/resources/reference-costs/#archive.

NHS Improvement. (2017b). "Reference Cost Collection: National Schedule of Reference Costs, 2016-17 - NHS trusts and NHS foundation trusts." from https://improvement.nhs.uk/resources/reference-costs/#archive.

NHS Scotland. (2020). "Our NHS Scotland website." Retrieved March, 2021, from http://www.ournhsscotland.com/.

NICE. (2009). "Appraising life-extending, end of life treatments." from https://www.nice.org.uk/guidance/gid-tag387/documents/appraising-life-extending-end-of-life-treatments-paper2.

NICE (2012). Methods for the development of NICE public health guidance (third edition) (PMG4), The National Institute for Health and Clinical Excellence.

NICE. (2013a). "Guide to the methods of technology appraisal 2013." from https://www.nice.org.uk/process/pmg9/resources/guide-to-the-methods-of-technology-appraisal-2013-pdf-2007975843781.

NICE. (2013b). "Guide to the methods of technology appraisal 2013. Process and methods." Retrieved August, 2020, from https://www.nice.org.uk/process/pmg9/chapter/foreword.

NICE. (2017). "Changes to NICE drug appraisals: what you need to know." Retrieved August, 2020, from https://www.nice.org.uk/news/feature/changes-to-nice-drug-appraisals-what-you-need-to-know.

NICE. (2019). "NICE technology appraisal guidance. Position statement on use of the EQ-5D-5L value set for England (updated October 2019)." Retrieved August, 2020, from https://www.nice.org.uk/about/what-we-do/our-programmes/nice-guidance/technology-appraisal-guidance/eq-5d-5l.

NICE. (2020a). "The National Institute for Health and Care Excellence (NICE). About.", from https://www.nice.org.uk/about.

NICE. (2020b). "The NICE glossary." Retrieved 2nd March, 2020, from https://www.nice.org.uk/glossary.

NICHSR. (2020). "HTA 101: V. Economic Analysis Methods." Retrieved August, 2020, from https://www.nlm.nih.gov/nichsr/hta101/ta10107.html.

Nora, Â. D., C. da Silva Rodrigues, R. de Oliveira Rocha, F. Z. M. Soares, M. Minatel Braga and T. L. Lenzi (2018). "Is Caries Associated with Negative Impact on Oral Health-Related Quality of Life of Pre-school Children? A Systematic Review and Meta-Analysis." Pediatric Dentistry **40**(7): 403-411.

O'Neill, C., H. V. Worthington, M. Donaldson, S. Birch, S. Noble, S. Killough, L. Murphy, M. Greer, J. Brodison, R. Verghis and M. Tickle (2017). "Cost-Effectiveness of Caries Prevention in Practice: A Randomized Controlled Trial." Journal of Dental Research **96**(8): 875-880.

O'Day, K. and D. J. Campbell (2016). "PRM207 - What's The Matter With Average Cost-Effectiveness Ratios? A Simple Graphical Explanation." Value in Health **19**(3): A107-A108.

O'Mahony, J. F., A. T. Newall and J. van Rosmalen (2015). "Dealing with Time in Health Economic Evaluation: Methodological Issues and Recommendations for Practice." PharmacoEconomics **33**(12): 1255-1268.

OECD (2015). Fiscal sustainability of health systems: bridging health and finance perspectives. Paris, The Organisation for Economic Co-operation and Development (OECD).

Office for National Statistics. (2020). "Healthcare expenditure, UK Health Accounts: 2018." Retrieved September, 2020, from https://www.ons.gov.uk/peoplepopulationandcommunity/healthandsocialcare/healthcaresystem/bulletins/ukhealthaccounts/2018#:~:text=Estimated%20healthcare%20spending%20per%20person,growth%20greatly%20exceeded%20population%20growth.

Owen, L., A. Morgan, A. Fischer, S. Ellis, A. Hoy and M. P. Kelly (2012). "The cost-effectiveness of public health interventions." Journal of Public Health **34**(1): 37-45.

Pahel, B., R. G. Rozier and G. Slade (2007). "Parental perceptions of children's oral health: The Early Childhood Oral Health Impact Scale (ECOHIS)." Health and Quality of Life Outcomes **5**(1): 6.

Pakdaman, A., S. J. Pourhashemi, M. Bagheri Ghalesalim, S. Ghadimi and Y. Bardaran Nakhjavani (2014). "Comparison of Children's Oral Health Related Quality of Life Pre- and Post Dental Treatment Under General Anesthesia Using F-ECOHIS Questionnaire." 2013 **24**(1): 121-122.

Pakpour, A. H., M. S. Yekaninejad, F. Zarei, F. Hashemi, M. M. Steele and J. W. Varni (2011). "The PedsQL TM Oral Health Scale in Iranian children: reliability and validity." International Journal of Paediatric Dentistry **21**(5): 342-352.

Pashaev, K. P. (1982). "[Economic effectiveness of dental caries prevention with fluorine preparations]." Stomatologiia **61**(1): 82-83.

Paton, N. I., W. Stohr, L. Oddershede, A. Arenas-Pinto, S. Walker, M. Sculpher and D. T. Dunn (2016). "The Protease Inhibitor Monotherapy Versus Ongoing Triple Therapy (PIVOT) trial: a randomised controlled trial of a protease inhibitor monotherapy strategy for long-term management of human immunodeficiency virus infection." Health Technol Assess **20**(21): 1-158.

Paulden, M. (2017). "Recent amendments to NICE's value-based assessment of health technologies: implicitly inequitable?" Expert Review of Pharmacoeconomics & Outcomes Research **17**(3): 239-242.

Payakachat, N., J. M. Tilford, E. Kovacs and K. Kuhlthau (2012). "Autism spectrum disorders: a review of measures for clinical, health services and cost-effectiveness applications." Expert Rev Pharmacoecon Outcomes Res **12**(4): 485-503.

Pedersen, A. B., E. M. Mikkelsen, D. Cronin-Fenton, N. R. Kristensen, T. M. Pham, L. Pedersen and I. Petersen (2017). "Missing data and multiple imputation in clinical epidemiological research." Clin Epidemiol **9**: 157-166.

PedsQL Website. (2020). "PedsQL Website: Publications section." Retrieved 3 April, 2020, from http://www.pedsql.org/PedsQL-Publications.doc.

Peres, M., L. Macpherson, R. Weyant, B. Daly, R. Venturelli, M. Mathur, S. Listl, R. Celeste, C. Guarnizo-Herreño, C. Kearns and H. Benzian (2019). "Oral diseases: a global public health challenge." Lancet **394**: 249-260.

Petersen-Ewert, C., M. Erhart and U. Ravens-Sieberer (2011). "Assessing health-related quality of life in European children and adolescents." Neuroscience & Biobehavioral Reviews **35**(8): 1752-1756.

Petersen, P. E. and H. Ogawa (2016). "Prevention of dental caries through the use of fluoride–the WHO approach." Community dent health **33**(2): 66-68.

Petrou, S. and A. Gray (2011). "Economic evaluation alongside randomised controlled trials: design, conduct, analysis, and reporting." BMJ (Clinical research ed.) **342**: d1548-d1548.

Phantumvanit, P., Y. Makino, H. Ogawa, A. Rugg-Gunn, P. Moynihan, P. E. Petersen, W. Evans, C. A. Feldens, E. Lo and M. H. Khoshnevisan (2018). "WHO global consultation on public health intervention against early childhood caries." Community dentistry and oral epidemiology **46**(3): 280-287.

Philips, Z., L. Bojke, M. Sculpher, K. Claxton and S. Golder (2006). "Good practice guidelines for decision-analytic modelling in health technology assessment." Pharmacoeconomics **24**(4): 355-371.

Phillips, C. (2009). What is cost-effectiveness? What is...? series. Health Economics., Hayward Group Ltd.

Pitts, N. B. and J. A. Davies (1988). Scottish Health Boards' Dental Epidemiological Programme Report of the 1987 / 1988 Survey of 5 Year Old Children. Dundee, University of Dundee.

Pitts, N. B. (2001). "Clinical diagnosis of dental caries: a European perspective." J Dent Educ **65**(10): 972-978.

Pitts, N. B., D. T. Zero, P. D. Marsh, K. Ekstrand, J. A. Weintraub, F. Ramos-Gomez, J. Tagami, S. Twetman, G. Tsakos and A. Ismail (2017). "Dental caries." Nature Reviews Disease Primers **3**(1): 17030.

Pokhrel, S. (2015). "Return on investment (ROI) modelling in public health: strengths and limitations." European Journal of Public Health **25**(6): 908-909.

Potapova, L. V. (1977). "[Medical and economic effectiveness of drinking water fluoridation in a district with an intensive dental caries affection in children]." Stomatologiia **56**(6): 16-21.

Prosser, L. A. (2009). "Current challenges and future research in measuring preferences for pediatric health outcomes." The Journal of pediatrics **155**(1): 7-9.

Public Health Advisory Committee (2014). RX058: Economic Analysis of Oral Health Improvement Programmes and Interventions.

Public Health England (2014). Local authorities improving oral health: commissioning better oral health for children and young people. An evidence-informed toolkit for local authorities. London, Public Health England.

Public Health England (2016a). National Dental Epidemiology Programme for England: oral health survey of five-year-old children 2015. A report on the prevalence and severity of dental decay. .

Public Health England. (2016b). "Return on investment of oral health improvement programmes for 0 to 5 year olds: infographic." Retrieved July, 2020, from https://assets.publishing.service.gov.uk/government/uploads/system/uploads/attachment_data/file/560973/ROI_oral_health_interventions.pdf.

Public Health England. (2016c). "Return on Investment of Oral Health Interventions Tool." from https://www.gov.uk/government/publications/improving-the-oral-health-of-children-cost-effective-commissioning.

Public Health England (2017). Return on Investment of Interventions for the Prevention and Treatment of Musculoskeletal Conditions. Final Report. London.

Public Health England. (2018a). "Guidance: Economic evaluation." Retrieved 05 May, 2020, from https://www.gov.uk/government/publications/evaluation-in-health-and-well-being-overview/economic-evaluation.

Public Health England. (2018b). "Health matters: health economics - making the most of your budget. (Guidance)." Retrieved September, 2020, from https://www.gov.uk/government/publications/health-matters-health-economics-making-the-most-of-your-budget/health-matters-health-economics-making-the-most-of-your-budget.

Pukallus, M., K. Plonka, S. Kularatna, L. Gordon, A. G. Barnett, L. Walsh and W. K. Seow (2013). "Cost-effectiveness of a telephone-delivered education programme to prevent early childhood caries in a disadvantaged area: a cohort study." BMJ Open **3**(5): 14.

Qu, Z., S. Zhang, C. Krauth and X. Liu (2019). "A systematic review of decision analytic modeling techniques for the economic evaluation of dental caries interventions." PLoS One **14**(5): e0216921.

Quinonez, R. B., S. C. Stearns, B. S. Talekar, R. G. Rozier and S. M. Downs (2006). "Simulating cost-effectiveness of fluoride varnish during well-child visits for Medicaid-enrolled children." Archives of Pediatrics & Adolescent Medicine **160**(2): 164-170.

Raat, H., A. D. Mohangoo and M. A. Grootenhuis (2006). "Pediatric health-related quality of life questionnaires in clinical trials." Current Opinion in Allergy and Clinical Immunology **6**(3): 180-185.

Rabarison, K. M., C. L. Bish, M. S. Massoudi and W. H. Giles (2015). "Economic evaluation enhances public health decision making." Frontiers in public health **3**: 164.

Raiklin, E. and B. Uyar (1996). "On the relativity of the concepts of needs, wants, scarcity and opportunity cost." International Journal of Social Economics.

Rajmil, L., M. Herdman, M.-J. Fernandez de Sanmamed, S. Detmar, J. Bruil, U. Ravens-Sieberer, M. Bullinger, M.-C. Simeoni and P. Auquier (2004). "Generic health-related quality of life instruments in children and adolescents: a qualitative analysis of content." Journal of Adolescent Health **34**(1): 37-45.

Ramos-Gomez, F. J. and D. S. Shepard (1999). "Cost-effectiveness model for prevention of early childhood caries." Journal of the California Dental Association **27**(7): 539-544.

Ravens-Sieberer, U., M. Erhart, N. Wille, R. Wetzel, J. Nickel and M. Bullinger (2006). "Generic Health-Related Quality-of-Life Assessment in Children and Adolescents." PharmacoEconomics **24**(12): 1199-1220.

Ravens-Sieberer, U., N. Wille, X. Badia, G. Bonsel, K. Burström, G. Cavrini, N. Devlin, A.-C. Egmar, N. Gusi, M. Herdman, J. Jelsma, P. Kind, P. R. Olivares, L. Scalone and W. Greiner (2010). "Feasibility, reliability, and validity of the EQ-5D-Y: results from a multinational study." Quality of Life Research **19**(6): 887-897.

Richardson, J., J. McKie and E. Bariola (2014). Multiattribute utility instruments and their use. Encyclopedia of health economics. A. J. Culyer. San Diego, Elsevier. **2:** 341-357.

Righolt, A. J., M. Jevdjevic, W. Marcenes and S. Listl (2018). "Global-, Regional-, and Country-Level Economic Impacts of Dental Diseases in 2015." Journal of Dental Research **97**(5): 501-507.

Riley, R. D., J. P. T. Higgins and J. J. Deeks (2011). "Interpretation of random effects meta-analyses." BMJ **342**: d549.

Robertson, R., L. Wenzel, J. Thompson and A. Charles (2017). Understanding NHS financial pressures. How are they affecting patient care? London, The King's Fund.

Rogers, H. J., H. D. Rodd, J. H. Vermaire, K. Stevens, R. Knapp, S. El Yousfi and Z. Marshman (2019). "A systematic review of the quality and scope of economic evaluations in child oral health research." Bmc Oral Health **19**.

Rogers, H. J., F. Gilchrist, Z. Marshman, H. D. Rodd and D. Rowen (2020). Selection and validation of a classification system for a child-centred caries-specific utility measure. Health Economics and Decision Science. Discussion Paper Series. Sheffield, The University of Sheffield. School of Health and Related Research.

Royal College of Nursing. (2016). "Pay scales for NHS nursing staff in England, Wales, Scotland and Northern Ireland from 1 April 2016. (Scotland figures, hourly rate.)." Retrieved 11 July, 2019, from https://www.rcn.org.uk/employment-and-pay/nhs-pay-scales-2016-17#tab3.

Rubin, D. B. (2004). Multiple Imputation for Nonresponse in Surveys, John Wiley & Sons.

Ruffin, R. J. and P. R. Gregory (1993). Principles of microeconomics, 5th ed. New York, Harper Collins.

Rugg-Gunn, A. J., C. L. Carmichael, A. D. French and J. A. Furness (1977). "Fluoridation in Newcastle and Northumberland. A clinical study of 5-year-old children." British Dental Journal **142**(12): 395-402.

Sabik, L. M. and R. K. Lie (2008). "Priority setting in health care: Lessons from the experiences of eight countries." International journal for equity in health **7**: 4-4.

Saigal, S., P. Rosenbaum, B. Stoskopf, L. Hoult, W. Furlong, D. Feeny and R. Hagan (2005). "Development, reliability and validity of a new measure of overall health for pre-school children." Quality of Life Research **14**(1): 243-252.

Samnaliev, M., R. Wijeratne, E. G. Kwon, H. Ohiomoba and M. W. Ng (2015). "Cost-effectiveness of a disease management program for early childhood caries." Journal of Public Health Dentistry **75**(1): 24-33.

Samuelson, P. (1948). Economics Columbus, OH, USA, McGraw-Hill.

Savage, M. F., J. Y. Lee, J. B. Kotch and W. F. Vann, Jr. (2004). "Early preventive dental visits: effects on subsequent utilization and costs." Pediatrics **114**(4): e418-423.

Schardt, C., M. B. Adams, T. Owens, S. Keitz and P. Fontelo (2007). "Utilization of the PICO framework to improve searching PubMed for clinical questions." BMC medical informatics and decision making **7**(1): 16.

Schmidt, L. J., A. M. Garrat and R. Fitzpatrick (2001). Instruments for children and adolescents: a review. Report to the Department of Health. Oxford, National Centre for Health Outcomes Development, University of Oxford.

Schmoeckel, J., K. Gorseta, C. H. Splieth and H. Juric (2020). "How to Intervene in the Caries Process: Early Childhood Caries – A Systematic Review." Caries Research.

Scott, J. (2000). "Children as respondents: The challenge for quantitative methods." Research with children: Perspectives and practices **2**: 87-108.

Scottish Dental Epidemiological Co-ordinating Committee (2003). Scotland's National Dental Inspections Programme 2003.

Scottish Government (2005). An Action Plan for Improving Oral Health and Modernising NHS Dental Services in Scotland. Edinburgh.

Scottish Government (2010a). The financial impact of early years interventions in Scotland Edinburgh.

Scottish Government (2010b). The financial impact of early years interventions in Scotland - Part 2. Edinburgh.

Scottish Government (2012a). HEAT Target 14/15 Child Fluoride Varnishing. Edinburgh The Scottish Government.

Scottish Government. (2012b). "Scottish Index of Multiple Deprivation 2012 - Executive Summary." from https://www.gov.scot/publications/scottish-index-multiple-deprivation-2012-executive-summary/.

Scottish Government (2012c). SIMD 2012 - Technical notes

Scottish Government. (2015). "Universal Health Visiting Pathway in Scotland – Pre-birth to Pre-school." Retrieved 22 April, 2020, from http://www.gov.scot/Publications/2015/10/9697/0.

Scottish Government (2016a). Fairer Scotland Action Plan. Edinburgh, The Scottish Government.

Scottish Government. (2016b). "The Scottish Index of Multiple Deprivation." Retrieved 22 April, 2020, from https://www2.gov.scot/Topics/Statistics/SIMD.

Scottish Government (2017). 2017-18 Outcomes Framework. Confirmation of Defined Outcomes and Performance Management Arrangements. (Letter to NHS Boards Chief Executives from the Director of Health Finance and Infrastructure, the Scottish Government). Edinburgh.

Scottish Government (2018). Review of Nutrition Requirements for Food and Drink in Schools (Scotland) Regulations 2008. Edinburgh, The Scottish Government.

Scottish Government. (2019a). "Early learning and childcare expansion - 2 year old eligibility: Business and regulatory impact assessment." Retrieved October,

2020, from https://www.gov.scot/publications/business-regulatory-impact-assessment-expansion-early-learning-childcare-2-year-old-eligibility/.

Scottish Government. (2019b, 13 Jun 2019). "Making school food healthier." Retrieved September, 2020, from https://www.gov.scot/news/making-school-food-healthier/.

Scottish Government (2019c). Summary statistics for schools in Scotland. Edinburgh.

SDNAP (2017). Scottish Dental Needs Assessment Programme (SDNAP). Oral Health and Dental Services for Children. Needs Assessment Report.

Selwitz, R. H., A. I. Ismail and N. B. Pitts (2007). "Dental caries." Lancet **369**(9555): 51-59.

Seow, W. K. (2018). "Early Childhood Caries." Pediatric Clinics of North America **65**(5): 941-954.

Shiell, A., C. Donaldson, C. Mitton and G. Currie (2002). "Health economic evaluation." Journal of epidemiology and community health **56**(2): 85.

Siegel, J. E., M. C. Weinstein, L. B. Russell and M. R. Gold (1996). "Recommendations for Reporting Cost-effectiveness Analyses." JAMA **276**(16): 1339-1341.

Simeoni, M. C., S. Schmidt, H. Muehlan, D. Debensason and M. Bullinger (2007). "Field testing of a European quality of life instrument for children and adolescents with chronic conditions: the 37-item DISABKIDS Chronic Generic Module." Qual Life Res **16**(5): 881-893.

Sischo, L. and H. L. Broder (2011). "Oral health-related quality of life: what, why, how, and future implications." Journal of dental research **90**(11): 1264-1270.

Skrepneka, G. H., E. L. Olveya and A. Sahaib (2012). "Econometric approaches in evaluating cost and utilization within pharmacoeconomic analyses." Pharmaceuticals Policy and Law **14**: 105–122.

Solans, M., S. Pane, M.-D. Estrada, V. Serra-Sutton, S. Berra, M. Herdman, J. Alonso and L. Rajmil (2008). "Health-Related Quality of Life Measurement in Children and Adolescents: A Systematic Review of Generic and Disease-Specific Instruments." Value in Health **11**(4): 742-764.

Stearns, S. C., R. G. Rozier, A. M. Kranz, B. T. Pahel and R. B. Quinonez (2012). "Cost-effectiveness of preventive oral health care in medical offices for young Medicaid enrollees." Archives of Pediatrics & Adolescent Medicine **166**(10): 945-951.

Steele, M. M., R. G. Steele and J. W. Varni (2009). "Reliability and Validity of the PedsQL™ Oral Health Scale: Measuring the Relationship Between Child Oral Health and Health-Related Quality of Life." Children's Health Care **38**(3): 228-244.

Stevens, K. (2009). "Developing a descriptive system for a new preference-based measure of health-related quality of life for children." Quality of Life Research **18**(8): 1105-1113.

Stevens, K. (2011). "Assessing the performance of a new generic measure of health-related quality of life for children and refining it for use in health state valuation." Appl Health Econ Health Policy **9**(3): 157-169.

Stevens, K. (2012). "Valuation of the Child Health Utility 9D Index." Pharmacoeconomics **30**(8): 729-747.

Suhrcke, M., D. M. Urban, K. Moesgaard Iburg, D. Schwappach, T. Boluarte and M. McKee (2007). The economic benefits of health and prevention in a high-income country: the example of Germany, WZB Discussion Paper.

The University of Sheffield. (2020). "Measuring and Valuing Health. SF-6D." Retrieved August, 2020, from https://www.sheffield.ac.uk/scharr/research/themes/valuing-health#SF-6D.

Thielen, F. W., G. A. P. G. Van Mastrigt, L. T. Burgers, W. M. Bramer, H. J. M. Majoie, S. M. A. A. Evers and J. Kleijnen (2016). "How to prepare a systematic review of economic evaluations for clinical practice guidelines: database selection and search strategy development (part 2/3)." Expert Review of Pharmacoeconomics & Outcomes Research **16**(6): 705-721.

Thokala, P., J. Ochalek, A. A. Leech and T. Tong (2018). "Cost-effectiveness thresholds: the past, the present and the future." Pharmacoeconomics **36**(5): 509-522.

Thompson, R. J., Jr., K. E. Gustafson, K. W. Hamlett and A. Spock (1992). "Psychological adjustment of children with cystic fibrosis: the role of child cognitive processes and maternal adjustment." J Pediatr Psychol **17**(6): 741-755.

Thorrington, D. and K. Eames (2015). "Measuring Health Utilities in Children and Adolescents: A Systematic Review of the Literature." PloS one **10**(8): e0135672-e0135672.

Tianviwat, S., V. Chongsuvivatwong and S. Birch (2008). "Prevention versus cure: Measuring parental preferences for sealants and fillings as treatments for childhood caries in Southern Thailand." Health Policy **86**(1): 64-71.

Tickle, M., M. Williams, T. Jenner and A. Blinkhorn (1999). "The effects of socioeconomic status and dental attendance on dental caries' experience, and treatment patterns in 5-year-old children." British Dental Journal **186**(3): 135-137.

Tickle, M., K. Milsom, D. King, P. Kearney-Mitchell and A. Blinkhorn (2002). "The fate of the carious primary teeth of children who regularly attend the general dental service." Br Dent J **192**(4): 219-223.

Tickle, M., A. S. Blinkhorn and K. M. Milsom (2008). "The occurrence of dental pain and extractions over a 3-year period in a cohort of children aged 3-6 years." J Public Health Dent **68**(2): 63-69.

Tickle, M., C. O'Neill, M. Donaldson, S. Birch, S. Noble, S. Killough, L. Murphy, M. Greer, J. Brodison, R. Verghis and H. V. Worthington (2016). "A randomised controlled trial to measure the effects and costs of a dental caries prevention regime for young children attending primary care dental services: the Northern Ireland Caries Prevention In Practice (NIC-PIP) trial." Health Technology Assessment (Winchester, England) **20**(71): 1-96.

Tinanoff, N., R. J. Baez, C. Diaz Guillory, K. J. Donly, C. A. Feldens, C. McGrath, P. Phantumvanit, N. B. Pitts, W. K. Seow, N. Sharkov, Y. Songpaisan and S. Twetman (2019). "Early childhood caries epidemiology, aetiology, risk assessment, societal burden, management, education, and policy: Global perspective." Int J Paediatr Dent **29**(3): 238-248.

Tonmukayakul, U., H. Calache, R. Clark, J. Wasiak and C. M. Faggion, Jr. (2015). "Systematic Review and Quality Appraisal of Economic Evaluation Publications in Dentistry." Journal of Dental Research **94**(10): 1348-1354.

Torrance, G. W., D. H. Feeny, W. J. Furlong, R. D. Barr, Y. Zhang and Q. Wang (1996). "Multiattribute utility function for a comprehensive health status classification system: Health Utilities Index Mark 2." Medical care: 702-722.

Trubman, A., S. L. Silberman and E. F. Meydrech (1991). "Treatment costs for carious primary teeth related to fluoride exposure." Journal of Dentistry for Children **58**(1): 69-71.

Tsakos, G. (2010). Oral health-related quality of life (OHRQoL) measurement in 5-year-olds in Glasgow: developing and evaluating a new OHRQoL measure: final report. London, University College London.

Tsakos, G., Y. I. Blair, H. Yusuf, W. Wright, R. G. Watt and L. M. Macpherson (2012). "Developing a new self-reported scale of oral health outcomes for 5-year-old children (SOHO-5)." Health Qual Life Outcomes **10**: 62.

Twetman, S., K. Boustedt, J. Roswall and J. Dahlgren (2020). "Systematic review suggests a relationship between moderate to late preterm birth and early childhood caries." Acta Paediatrica **n/a**(n/a).

van Mastrigt, G. A., M. Hiligsmann, J. J. Arts, P. H. Broos, J. Kleijnen, S. M. Evers and M. H. Majoie (2016). "How to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions: a five-step approach (part 1/3)." Expert Review of Pharmacoeconomics & Outcomes Research **16**(6): 689-704.

Varni, J. W., C. A. Limbers and T. M. Burwinkle (2007). "Parent proxy-report of their children's health-related quality of life: an analysis of 13,878 parents' reliability and validity across age subgroups using the PedsQL 4.0 Generic Core Scales." Health and quality of life outcomes **5**: 2-2.

Varni, J. W. (2017). Scaling and scoring of the Pediatric Quality of Life Inventory, PedsQL.

Varni, J. W. (2019). "PedsQL Website." from https://www.pedsql.org/index.html.

Varni, J. W. (2020). "PedsQL Website: About the Model." Retrieved 3 April, 2020, from http://www.pedsql.org/about_pedsql.html.

Vernazza, C., P. Heasman, F. Gaunt and M. Pennington (2012). "How to measure the cost-effectiveness of periodontal treatments." Periodontology 2000 **60**(1): 138-146.

Versloot, J., J. Veerkamp and J. Hoogstraten (2004). "Dental Discomfort Questionnaire: predicting toothache in preverbal children." European journal of paediatric dentistry **5**: 170-173.

Verstraete, J., A. Lloyd, D. Scott and J. Jelsma (2020a). "How does the EQ-5D-Y Proxy version 1 perform in 3, 4 and 5-year-old children?" Health and Quality of Life Outcomes **18**(1): 149.

Verstraete, J., L. Ramma and J. Jelsma (2020b). "Item generation for a proxy health related quality of life measure in very young children." Health and Quality of Life Outcomes **18**(1): 11.

von Philipsborn, P., J. M. Stratil, J. Burns, L. K. Busert, L. M. Pfadenhauer, S. Polus, C. Holzapfel, H. Hauner and E. Rehfuess (2019). "Environmental interventions to reduce the consumption of sugar-sweetened beverages and their effects on health." The Cochrane database of systematic reviews **6**(6): CD012292-CD012292.

Wallander, J. L., M. Schmitt and H. M. Koot (2001). "Quality of life measurement in children and adolescents: Issues, instruments, and applications." Journal of Clinical Psychology **57**(4): 571-585.

Walsh, T., H. V. Worthington, A. M. Glenny, V. C. C. Marinho and A. Jeroncic (2019). "Fluoride toothpastes of different concentrations for preventing dental caries." Cochrane Database of Systematic Reviews(3).

Walter, E. and S. Zehetmayr (2006). Guidelines on Health Economic Evaluations (Consensus Paper) I. f. P. Research. Vienna.

Wanless, D. (2004). Securing good health for the whole population. Final report. . London, HM Treasury.

Watt, R. G., R. Harnett, B. Daly, S. S. Fuller, E. Kay, A. Morgan, P. Munday, R. Nowjack-Raymer and E. T. Treasure (2004). The Oral Health Promotion Evaluation Toolkit. London, Stephen Hancocks Ltd; London.

Watt, R. G. (2007). "From victim blaming to upstream action: tackling the social determinants of oral health inequalities." Community Dentistry and Oral Epidemiology **35**(1): 1-11.

Watt, R. G. and A. Sheiham (2012). "Integrating the common risk factor approach into a social determinants framework." Community Dentistry and Oral Epidemiology **40**(4): 289-296.

Watt, R. G. (2012). "Social determinants of oral health inequalities: implications for action." Community Dentistry and Oral Epidemiology **40**(s2): 44-48.

Watt, R. G., M. R. Mathur, J. Aida, M. Bönecker, R. Venturelli and S. A. Gansky (2018). "Oral health disparities in children: a canary in the coalmine?" Pediatric Clinics **65**(5): 965-979.

Watt, R. G., B. Daly, P. Allison, L. M. D. Macpherson, R. Venturelli, S. Listl, R. J. Weyant, M. R. Mathur, C. C. Guarnizo-Herreno, R. K. Celeste, M. A. Peres, C. Kearns and H. Benzian (2019). "Ending the neglect of global oral health: time for radical action." Lancet **394**(10194): 261-272.

Watts, J. J. and L. Segal (2009). "Market failure, policy failure and other distortions in chronic disease markets." BMC Health Services Research **9**(1): 102.

Watts, R. D. and I. W. Li (2019). "Use of Checklists in Reviews of Health Economic Evaluations, 2010 to 2018." Value in Health **22**(3): 377-382.

WCRF (2015). Curbing global sugar consumption. Effective food policy actions to help promote healthy diets & tackle obesity. London, World Cancer Research Fund International (WCRF)

Weatherly, H., M. Drummond, K. Claxton, R. Cookson, B. Ferguson, C. Godfrey, N. Rice, M. Sculpher and A. Sowden (2009). "Methods for assessing the cost-effectiveness of public health interventions: key challenges and recommendations." Health Policy **93**(2-3): 85-92.

Webb, N. J., R. L. Woolley, T. Lambe, E. Frew, E. A. Brettell, E. N. Barsoum, R. S. Trompeter, C. Cummins, K. Wheatley and N. J. Ives (2019). "Sixteen-week versus standard eight-week prednisolone therapy for childhood nephrotic syndrome: the PREDNOS RCT." Health Technol Assess **23**(26): 1-108.

Wennhall, I., A. Norlund, L. Matsson and S. Twetman (2010). "Cost-analysis of an oral health outreach program for preschool children in a low socioeconomic multicultural area in Sweden." Swedish Dental Journal **34**(1): 1-7.

White, I. R., P. Royston and A. M. Wood (2011). "Multiple imputation using chained equations: Issues and guidance for practice." Statistics in Medicine **30**(4): 377-399.

White, S. (2017). "Health Matters: Child dental health." Public health matters. (The official blog of Public Health England.) https://publichealthmatters.blog.gov.uk/2017/06/14/health-matters-child-dental-health/ 2019.

Whitehead, S. J. and S. Ali (2010). "Health outcomes in economic evaluation: the QALY and utilities." British Medical Bulletin **96**(1): 5-21.

WHO (2015). Promoting Health, Preventing Disease the Economic Case: The Economic Case, OECD Publishing.

WHO (2017a). Sugars and dental caries. WHO technical information note. October 2017., World Health Organization.

WHO (2017b). World Health Organization. WHO expert consultation on public health intervention against early childhood caries: report of a meeting, Bangkok, Thailand, 26-28 January 2016. Geneva, World Health Organisation.

WHO (2019). Ending childhood dental caries: WHO implementation manual, World Health Organization.

WHO. (2020a). "Analysing Disrupted Health Sectors - A Modular Manual. Module 6. Analysing Health Sector Financing and Expenditure. Annex 6b: Costs and Cost Analysis." Retrieved August, 2020, from https://www.who.int/hac/techguidance/tools/disrupted_sectors/module_06/en/index10.html.

WHO. (2020b). "Metrics: Disability-Adjusted Life Year (DALY)." Retrieved August, 2020, from https://www.who.int/healthinfo/global_burden_disease/metrics_daly/en/.

Widenheim, J. and D. Birkhed (1991). "Caries-preventive effect on primary and permanent teeth and cost-effectiveness of an NaF tablet preschool program." Community Dentistry & Oral Epidemiology **19**(2): 88-92.

Wijnen, B., G. Van Mastrigt, W. K. Redekop, H. Majoie, R. De Kinderen and S. Evers (2016). "How to prepare a systematic review of economic evaluations for informing evidence-based healthcare decisions: data extraction, risk of bias, and transferability (part 3/3)." Expert Review of Pharmacoeconomics & Outcomes Research **16**(6): 723-732.

Wilkinson, G., B. Hesdon, D. Wild, R. Cookson, C. Farina, V. Sharma, R. Fitzpatrick and C. Jenkinson (2000). "Self-report quality of life measure for people with schizophrenia: the SQLS." The British Journal of Psychiatry **177**(1): 42-46.

Wille, N., X. Badia, G. Bonsel, K. Burström, G. Cavrini, N. Devlin, A.-C. Egmar, W. Greiner, N. Gusi, M. Herdman, J. Jelsma, P. Kind, L. Scalone and U. Ravens-Sieberer (2010a). "Development of the EQ-5D-Y: a child-friendly version of the EQ-5D." Quality of Life Research **19**(6): 875-886.

Wille, N., X. Badia, G. Bonsel, K. Burström, G. Cavrini, N. Devlin, A. C. Egmar, W. Greiner, N. Gusi, M. Herdman, J. Jelsma, P. Kind, L. Scalone and U. Ravens-Sieberer (2010b). "Development of the EQ-5D-Y: a child-friendly version of the EQ-5D." Qual Life Res **19**(6): 875-886.

Wilson, N., A. Davies, N. Brewer, N. Nghiem, L. Cobiac and T. Blakely (2019). "Can cost-effectiveness results be combined into a coherent league table? Case study from one high-income country." Population Health Metrics **17**(1): 10.

Wohlin, C. (2014). Guidelines for snowballing in systematic literature studies and a replication in software engineering. Proceedings of the 18th international conference on evaluation and assessment in software engineering.

Wong, H. M., C. P. J. McGrath, N. M. King and E. C. M. Lo (2011). "Oral Health-Related Quality of Life in Hong Kong Preschool Children." Caries Research **45**(4): 370-376.

Wright, W., S. Turner, Y. Anopa, E. McIntosh, O. Wu, D. I. Conway, L. M. D. Macpherson and A. D. McMahon (2015). "Comparison of the caries-protective effect of fluoride varnish with treatment as usual in nursery school attendees receiving preventive oral health support through the Childsmile oral health improvement programme - the Protecting Teeth@3 Study: a randomised controlled trial." Bmc Oral Health **15**.

Yeung, C. A., L. Y. Chong and A. M. Glenny (2015). "Fluoridated milk for preventing dental caries." Cochrane Database of Systematic Reviews(8).

York Health Economics Consortium. (2016a). "Glossary. Health Economic Terms. Cost-effectiveness plane." Retrieved 06 May, 2020, from https://yhec.co.uk/glossary/cost-effectiveness-plane/.

York Health Economics Consortium. (2016b). "Glossary. Health Economic Terms. Cost Minimisation Analysis." Retrieved August, 2020, from https://yhec.co.uk/glossary/cost-minimisation-analysis/.

York Health Economics Consortium. (2016c). "Glossary. Health Economic Terms. Preference-Based Measures." Retrieved August, 2020, from https://yhec.co.uk/glossary/preference-based-measures/.

York Health Economics Consortium. (2016d). "Glossary. Health Economic Terms. Time Horizon." Retrieved August, 2020, from https://yhec.co.uk/glossary/time-horizon/.

York Health Economics Consortium (2016e). "A rapid review of evidence on the cost-effectiveness of interventions to improve the oral health of children aged 0-5 years." London: Public Health England.

Zaror, C., Y. Pardo, G. Espinoza-Espinoza, À. Pont, P. Muñoz-Millán, M. J. Martínez-Zapata, G. Vilagut, C. G. Forero, O. Garin, J. Alonso and M. Ferrer (2019). "Assessing oral health-related quality of life in children and adolescents: a systematic review and standardized comparison of available instruments." Clinical Oral Investigations **23**(1): 65-79.

Zavras, A. I., B. L. Edelstein and A. Vamvakidis (2000). "Health care savings from microbiological caries risk screening of toddlers: a cost estimation model." Journal of Public Health Dentistry **60**(3): 182-188.

Zöllner, H. F., G. Stoddart, C. Selby Smith and W. H. Organization (2003). Learning to live with Health Economics, Copenhagen: WHO Regional Office for Europe.