Evaluation of electronic cigarettes for smoking cessation in patients with periodontitis

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Abstract

Background

Smoking cessation interventions play an important role in dental care, especially for patients with periodontitis. Novel nicotine products, such as electronic cigarettes (e-cigarettes), have recently become popular with smokers and can be used to quit or reduce tobacco smoking.

Aims/objectives

This research aimed to explore the behavioural and biological changes that occur when smokers with periodontitis are provided with an e-cigarette.

Methods

This research had three components. Firstly, a systematic review investigated the *in vitro* effects of nicotine on periodontal cells. Secondly, a 6-month pilot randomised controlled trial (RCT) was conducted of an e-cigarette smoking cessation intervention in smokers with periodontitis. Outcome measures were collected on both smoking status and oral health. The main focus was on feasibility, including recruitment and retention rates. Thirdly, theory-based qualitative interviews investigated patient perceptions about smoking, dental smoking cessation interventions and e-cigarettes.

Results

The systematic review concluded that nicotine, at physiological concentrations, was not cytotoxic to periodontal cells *in vitro*. Nicotine may have effects on other cell functions although evidence was contradictory. In the pilot RCT, 80 smokers with periodontitis were recruited in 15 months. Participant retention was 73% at 6 months. The e-cigarette intervention was well received with 90% using an e-cigarette at the quit date. 20% of participants in the control group used an e-cigarette, against instructions. Outcome measures were successfully completed. A weekly smoking questionnaire had poor completion rates. Several factors were perceived to influence smoking behaviour in individuals with periodontitis. These patients perceived dentist-delivered smoking cessation advice positively. General perceptions of e-cigarettes were mixed and influenced by personal experience, other users, addiction concerns, health concerns and social acceptability.

Conclusions

Providing and studying an e-cigarette intervention within the dental setting was feasible and well accepted by patients. Insights were gained into perceived influences on smoking behaviour and how to best conduct future research.

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Candidate statement

I wish to acknowledge the help and contribution I have received throughout my PhD studies.

My supervisors were involved in planning, organisation and guidance throughout all aspects of the projects.

Chapter 2: Systematic review

Professor Philip Preshaw (PP) and James Campbell (JC) provided assistance with this systematic review. I, Richard Holliday (RH), conceived the research idea, JC assisted with literature searching and data extraction and all the authors (RH, PP, and JC) contributed towards the analysis and critically reviewed the manuscript. Statistical advice was provided by Andy Bryant.

Chapter 3: Feasibility Randomised Controlled Trial

The Newcastle Clinical Trials Unit (CTU) provided advice and guidance during the design and planning stages of the research study. The Dental Clinical Research Facility Team played a critical role in delivering the clinical aspects of this research study. Kerry Stone (KS), Kimberley Pickering and Ashleigh Stone provided research dental nursing support. Jennifer Wilkinson provided data entry services. KS and RH audited the data entry. Nichola Lansdowne collected the blinded clinical data. A Trial Oversight Committee (TOC) provided overview and support throughout the study. The independent TOC members comprised: Professor Val Clerehugh, Dawn Teare, Stuart Healey and Chris Burnett.

Chapter 4 & 5: Participant interviews

Suzanne McDonald helped design the interviews, provided support during the study, second coded and provided guidance during analysis and interpretation. Interview transcription was conducted by David Anderson of Fairway Business Services.

The rest of this PhD work was conducted by myself.

Publications

Aspects of this thesis are based upon published work:

Published papers

Holliday, R, Corson, M. and Horridge, C. 2014. Electronic cigarettes: harm reduction or another addiction?; the dental perspective. *Dental Update.* 41:667-676.

Holliday, R, and Stubbs, C. 2015. The Dental Perspective on Electronic Cigarettes: the good, the bad and the ugly. *Oral Health Journal*, 16-26.

Holliday, R, Kist, R, and Bauld, L. 2016. E-cigarette vapour is not inert and exposure can lead to cell damage. *Evidence-Based Dentistry.* 17:2-3. DOI: 10.1038/sj.ebd.6401143.

Holliday, R, Amin, K, Lawrence, V, and Preshaw, PM. 2017. Tobacco education in UK dental schools: A survey of current practice. *European Journal of Dental Education.* 22:e248-e252. DOI: 10.1111/eje.12280.

Holliday, R, Preshaw, PM, and Bauld, L. 2017. Smoking cessation: The role of e-cigarettes. *British Dental Journal.* 222:3. DOI: 10.1038/sj.bdj.2017.6.

Holliday, R, Kist, R, Bauld, L, and Preshaw, PM. 2017. E-cigarettes and oral health: a balanced viewpoint. *Oral Diseases.* 23:1180-1181. DOI: 10.1111/odi.12666.

Ahmed, Z, Preshaw, PM, Bauld, L, and **Holliday, R**. 2018. Dental professionals' opinions and knowledge of smoking cessation and electronic cigarettes: a cross-sectional survey in the north of England. *British Dental Journal.* (In press).

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Book chapter

Preshaw, PM, Chambrone, L, and **Holliday, R.** 2018. Smoking and Periodontal Disease, in Newman, T. and Carranza, K. (Thirteenth Edition) Clinical Periodontology. Philadelphia: Elsevier, pp. 181-189 and online case scenario available at: www.expertconsult.com (Accessed: 11/08/2018)

Other outputs

Holliday, R. 2017. Written evidence submitted by Dr Richard Holliday (ECG0036) on e-cigarettes and oral health, House of Commons Select Science and Technology Committee on E-cigarettes. [Online] Available at: http://data.parliament.uk/writtenevidence/committeeevidence.svc/evidencedocument/science-and-technology-committee/ecigarettes/written/75221.html (Accessed: 11/08/2018)

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List of Abbreviations

AE	Adverse Event
ASH	Action on Smoking and Health
BOP	Bleeding on Probing
COMET	Core Outcome Measures in Effectiveness Trials
CONSORT	Consolidated Standards of Reporting Trials
CAL	Clinical Attachment Level
CTU	Clinical Trials Unit
COREQ	COnsolidating criteria for REporting Qualitative research
CODS	Clinical Oral Dryness Score
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of an Investigational Medicinal Product
CRF	Case Report Form
DCRF	Dental Clinical Research Facility
DIY	Do it yourself
eCO	Expired air Carbon Monoxide
ED_{50}	Effective Dose (median)
EEA	European Economic Area
EU	European Union
FTND	Fagerstroms Test of Nicotine Dependence
FMD	Full Mouth Debridement
FTA	Failed To Attend
GMP	General Medical Practitioner
GRAS	Generally Recognised As Safe
GRO	Growth-Regulating Oncogene
HCPs	Healthcare Professionals
HGECs	Human Gingival Epithelial Cells
HGFs	Human Gingival Fibroblasts
HPDLCs	Human Periodontal Ligament Cells
HOECs	Human Oral Epithelial Cells
HRA	Health Research Authority
IB	Inflammatory Biomarkers
IC_{50}	Inhibitory Concentration (median)

ICH	International Conference on Harmonisation
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
IQR	Interquartile Range
IL	Interleukin
IRAS	Integrated Research Approval System
ISRCTN	International Standard Randomised Controlled Trial Number
LQ	Lower Quartile
MGI	Modified Gingival Index
MHRA	Medicines and Healthcare products Regulatory Agency
Micro	Microbiological outcome measure
MMP	Matrix Metalloproteinase
MPSs	Mood and Physical Symptoms SCale
NCSCT	National Centre for Smoking Cessation and Training
NDA	Non-disclosure Agreement
NDH	Newcastle Dental Hospital
NICE	National Institute of Clinical Excellence
NIHR	National Institute for Health Research
NHANES	National Health and Nutrition Examination Survey
NHS	National Health Service
NRT	Nicotine Replacement Therapy
NuTH	Newcastle upon Tyne NHS Hospitals Foundation Trust
OHI	Oral Hygiene Instruction
OHQoL-UK	UK Oral Health related Quality of Life measure
PDL	Periodontal Ligament
PESA	Periodontal Epithelial Surface Area
PI	Plaque Index
PIC	Participant Identifying Centre
PIS	Participant Information Sheet
PISA	Periodontal Inflammed Surface Area
PG	Propylene Glycol
PGE_2	Prostaglandin E2
PHE	Public Health England
PPD	Pocket Probing Depth

PRECIS-2	PRagmatic Explanatory Continuum Indicator Summary 2
REC	Research Ethics Committee
RCT	Randomised Controlled Trial
RR	Relative Risk
RS6-eCO	Russell Standard 6-month quitter based upon expired air Carbon Monoxide
RS6-S	Russell Standard 6-month quitter based upon expired air Carbon Monoxide and salivary analysis
SA	Salivary Anabasine
SAE	Serious Adverse Event
SC	Salivary Cotinine
SCA	Smoking Cessation Advice
SD	Standard Deviation
SMS	Short Message Service
SOP	Standard Operating Procedure
SPT	Supportive Periodontal Therapy
StR	Speciality Registrar
TDF	Theory Domains Framework
TiDieR	Template for Intervention Description and Replication
TIMP	Tissue Inhibitors of Metalloproteinases
TOC	Trial Oversight Committee
TPD	Tobacco Products Directive
VBA	Very Brief Advice
VG	Vegetable Glycerin
UNC-15	University of North Carolina-15
UQ	Upper Quartile
US	United States

Chapter 1. Literature Review

Prologue

Dental professionals have an important role in supporting their patients to stop smoking by providing smoking cessation interventions. Many oral diseases are linked to tobacco smoking and dental treatments have improved outcomes if smokers quit. Electronic cigarettes (e-cigarettes) have become common among smokers and ex-smokers and the implications for oral health need to be investigated, including their role as a smoking cessation aid as well as the potential effects on the oral tissues and treatment outcomes.

This literature review opens with an overview of the historical and current situation of tobacco smoking and disease burden. Mechanisms of smoking-related oral diseases are then considered, with particular focus on periodontal diseases. Next, methods of smoking cessation, both generally and within the dental setting, are discussed. The development of e-cigarettes is then explored, including the possible oral health implications.

1.1 Tobacco smoking

1.1.1 *Epidemiology and the smoking epidemic*

Tobacco smoking killed 100 million people worldwide in the 20th century and is still the single greatest preventable cause of death worldwide (World Health Organisation, 2008). The World Health Organisation (WHO) predicts that tobacco-related mortality could reach one billion (cumulatively) during the 21st century (World Health Organisation, 2008). Global smoking rates are around 15% with over 1.1 billion smokers in 2015 (World Health Organisation, 2015).

Within the UK, tobacco smoking peaked around the middle of the 20th century. The first available data (industry figures) reports the peak of male smoking in 1948 at 81%, with female smoking peaking in 1966 (and 1969) at 44% (Royal College of Physicians, 2000). Independent data were collected from 1972 and demonstrated a progressive decline in both sexes, occurring at the fastest rate during the 1970s and 1980s (Royal College of Physicians, 2000). Since then there has been a continued decline but at a slower rate, sometimes almost plateauing (Action on Smoking and Health, 2017c). The most recent data, from 2017, reported 15.1% of UK adults as current smokers (Office of National Statistics, 2018b).

Lopez *et al.* (1994) proposed a 100-year, four-stage model for the smoking epidemic in developed countries, portrayed in Figure 1.1. Many developed countries, such as the UK and US, are now in stage IV of the model, where smoking prevalence rates are decreasing in both sexes and smoking-related deaths have peaked but are starting to decline. Global attention is now focusing on developing countries in the earlier stages of the smoking epidemic. The WHO predict that 80% of the 8 million annual smoking-related deaths will occur in developing countries by 2023 (World Health Organisation, 2008).

Developed countries at stage IV of the tobacco epidemic are now discussing ‘smokefree’ goals. A number of countries have set ambitious targets to reduce smoking prevalence rates to five percent or below: New Zealand by 2025 (New Zealand Government, 2011), Scotland by 2034 (The Scottish Government, 2013), and Canada by 2035 (Health Canada, 2017). England’s most recent policy is somewhat less ambitious, aiming to achieve smoking prevalence of 12% or less by 2022 (Department of Health, 2017). Often the ‘tobacco endgame’ concept is discussed; this is a chess analogy, whereby, with fewer pieces on the board, it is necessary to change tactics to win (McDaniel *et al.*, 2016). This endgame vision goes beyond ‘business as usual’ and requires radical strategies, moving from controlling to ending the tobacco epidemic (McDaniel *et al.*, 2016). Four broad target areas of potential

strategies have been proposed: products (make cigarettes less appealing or displace with less harmful alternatives), users (restrict access, introduce licences/prescriptions), market mechanisms (reduce availability or impose a ban), and structural (state takeover of tobacco companies) (McDaniel *et al.*, 2016). Many countries are now 'racing' to be the first to achieve smokefree status.

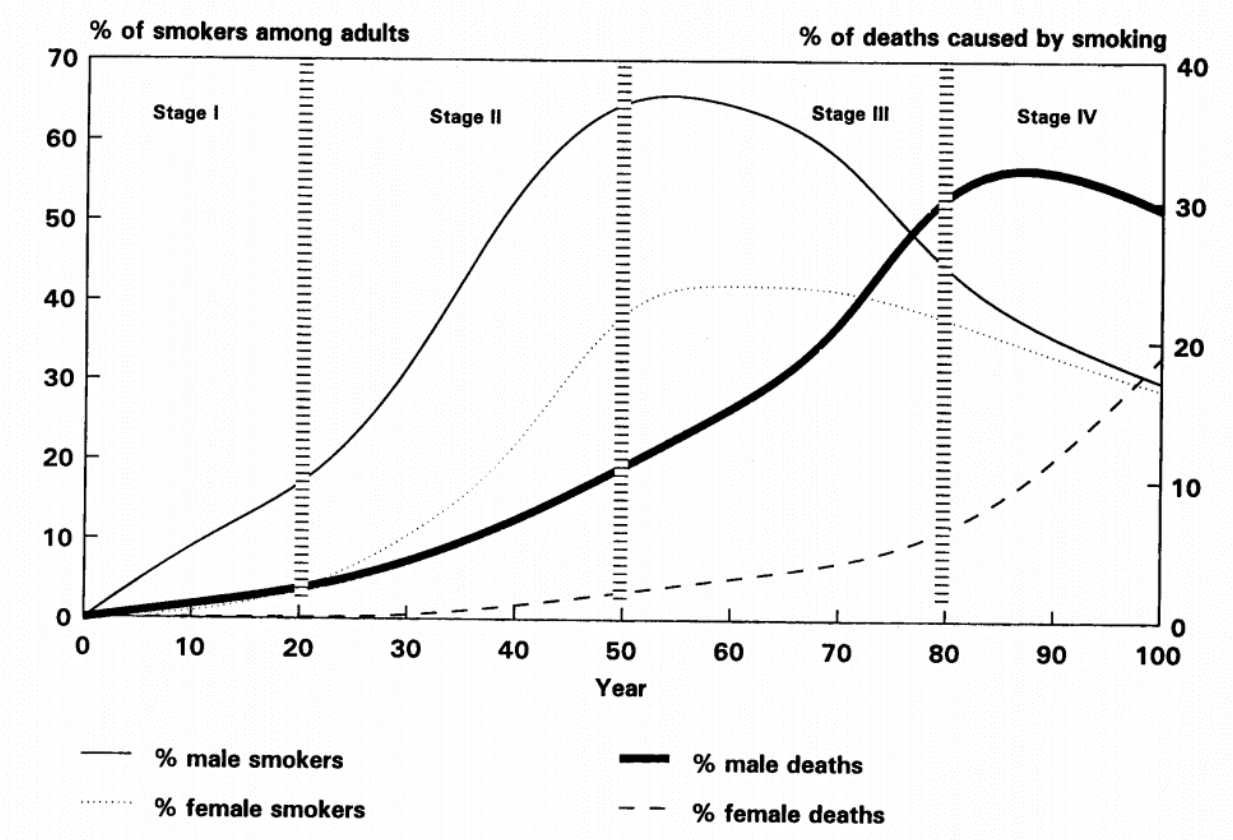

Figure 1.1 Model of the smoking epidemic in developed countries.

Reproduced from Lopez *et al.* (1994). Four stages of the smoking epidemic were proposed. Stage 1: both male and females have low smoking prevalence for 1-2 decades as smoking becomes socially acceptable. Stage 2: male smoking prevalence rises to a peak in the range 50-80%; female smoking prevalence lags behind that of males by 1-2 decades; stage spans 2-3 decades; male smoking-attributable deaths reach 10% by the end of this stage. Stage 3: male smoking prevalence rates decline; female smoking prevalence rates peak at 35-45%; male smoking-attributable deaths rise to 25-30%; female smoking-attributable deaths around 5%; stage lasts 3 decades. Stage 4: Both male and female smoking prevalence rates slowly decline; male smoking-attributable deaths peak at 30-35%, then decline; female smoking-attributable deaths rise rapidly.

1.1.2 *Nicotine and tobacco addiction*

Nicotine biochemistry

Nicotine is an alkaloid present naturally in tobacco leaves, acting as a botanical insecticide (Benowitz *et al.*, 2009). During tobacco combustion, the nicotine is distilled and carried on tar droplets into the user's body. Nicotine is absorbed across biological membranes, especially the small airways and alveoli, but sometimes in the mouth depending on the pH of the smoke and ratio of ionised:unionised nicotine (Benowitz *et al.*, 2009). High levels of nicotine reach the brain in a matter of seconds, producing rapid behaviour reinforcement and contributing to the well-known addictiveness of tobacco smoking (Benowitz, 1990). Nicotinic cholinergic receptors are stimulated to release a variety of neurotransmitters, including dopamine, which signals a pleasurable experience (Benowitz, 2010). Chewing tobaccos, snuff and nicotine replacement therapies (NRT) have a buffered alkaline pH. This facilitates nicotine absorption through the membrane linings such as the buccal mucosa in the mouth, leading to much slower absorption (West *et al.*, 2000), with any swallowed nicotine being subjected to first-pass metabolism (Benowitz *et al.*, 1987; Benowitz *et al.*, 2009). Transdermal NRT patches rely on the knowledge that nicotine base is well absorbed through skin.

Nicotine has sympathomimetic effects such as increasing the heart rate and transiently increasing blood pressure (Benowitz, 2003). However, nicotine has not been associated with any significant general health harms, is categorised as a non-carcinogen (World Health Organisation, 2014), and has been used in the form of NRT for several decades (Stead *et al.*, 2012). Preclinical studies have suggested potential therapeutic roles in psychiatric conditions such as Alzheimer's disease and post-traumatic stress disorder (Moran, 2012).

Nicotine has a relatively short half-life (2 hours) and is converted to six main metabolites (Benowitz *et al.*, 2009). In humans, 70-80% is converted to cotinine, which has a much longer half-life (16 hours) than nicotine, making it a useful biomarker for nicotine intake (Benowitz *et al.*, 2009). Cotinine has different biological effects to nicotine, being non-addictive and without cardiovascular effects (Barreto *et al.*, 2015).

Addiction

Addiction can be defined as the compulsive use of a substance despite harmful consequences, characterised by the inability to stop using it (National Institute on Drug Abuse, 2018). Physical dependence refers to the body's reliance on an external source of the substance to avoid withdrawal symptoms. Often addiction and physical dependence coexist and can be

hard to distinguish. The addictive potential of pure nicotine is weak (Scientific Committee on Emerging and Newly Identified Health Risks (SCENIHR), 2010), however, when delivered in a tobacco cigarette it is highly addictive (Royal College of Physicians, 2016). Many aspects of tobacco cigarette product design enhance nicotine delivery and uptake. For example, several substances are added including: monoamine oxidase inhibitors, which enhance the motivational properties of nicotine; sugar and polysaccharides, which form further addictive compounds that also act synergistically with nicotine; menthol, which increases the palatability of smoke, facilitating deeper inhalation and higher nicotine intake; cocoa and chocolate, which contain theobromine, a bronchodilator; levulinic acid, which is addictive in itself but also increases the palatability of smoke; and alkaline additives which optimise the pH of the smoke and again enhance nicotine absorption (Benowitz, 2010). Tobacco addiction occurs when users rely on smoking to modulate mood and arousal, relieve withdrawal symptoms, or both (Benowitz, 2010). Tobacco addiction is more complex than simply nicotine addiction and involves positive reinforcements, conditioning, neuroadaptation, genetic predisposition and vulnerability to addiction (Benowitz, 2010). In the context of traditional NRTs, there is a relatively low potential for physical dependence or addiction, mainly because of the route of administration and comparatively slow nicotine delivery to the brain (Le Houezec, 2003).

1.1.3 *Smoking-induced diseases*

The detrimental health effects of smoking have been extensively studied following the landmark 'British Doctors Study' initiated in 1951. This followed over forty thousand medical doctors and was the first prospective study to convincingly link tobacco smoking with risk of death from lung cancer, myocardial infarction and chronic obstructive pulmonary disease (COPD) (Doll and Hill, 1954; Doll and Hill, 1956). The study later went on to demonstrate the life-long effects of smoking with over 50 years of follow up (Doll *et al.*, 2004). A key finding was that lifelong smokers had a 50% chance of dying prematurely from a complication of smoking (Doll *et al.*, 2004). Quitting at any age resulted in benefits e.g. a 60-year-old smoker who quit would gain an additional three years of life (Doll *et al.*, 2004). Subsequently, smoking has been linked to a wide range of diseases and conditions including: cancers, respiratory and circulatory diseases, stomach and duodenal ulcers, erectile dysfunction, infertility, osteoporosis, cataracts, periodontitis, pregnancy complications and birth defects (The National Institute for Health and Care Excellence, 2013a). Smokers have poorer quality of life as measured on several scales with significant improvement following cessation (Goldenberg *et al.*, 2014).

There is significant health inequality with smoking being the primary reason for the gap in healthy life expectancy between the highest and lowest socioeconomic groups in western society (Jha *et al.*, 2006). Within the lowest socioeconomic groups, smoking was responsible for almost half of the total male mortality during the 1990s (Jha *et al.*, 2006). Smoking prevalence rates exist on a social gradient with higher smoking rates in lower socioeconomic groups (Amos *et al.*, 2011). These so-called disadvantaged smokers have a higher level of cigarette consumption and although they are equally likely as those of higher socio-economic status to make a quit attempt, they are less likely to be successful (Amos *et al.*, 2011). Tobacco control measures need to be designed to reduce socioeconomic inequalities; a recent review concluded that increasing tobacco price via tax had the greatest potential (Hill *et al.*, 2014).

Tobacco smokers are at increased risk of poorer health, poorer quality of life and increased mortality. Oral health is an important aspect of this, with the mouth being the first contact point for tobacco smoke when it enters the body, when the smoke is at its hottest and most concentrated. Many oral diseases and conditions have been associated with tobacco smoking, such as: oral potentially malignant disorders, oral cancer, periodontitis, peri-implantitis, acute necrotising ulcerative gingivitis, oral mucosa diseases (candidosis, melanosis), dental caries, alveolar osteitis (dry sockets), staining and halitosis. The investigations presented in this thesis focus on periodontitis and hence the literature review will focus on this in subsequent sections.

1.2 **Periodontitis and tobacco smoking**

1.2.1 ***Definition and classification of periodontal diseases***

Periodontal diseases (gum diseases) are some of the most common inflammatory conditions in humans (Kassebaum *et al.*, 2014). Periodontitis, an advanced form of periodontal disease, has a multifactorial aetiology but the principal process involves a dental plaque biofilm accumulating in the subgingival environment causing an immune and inflammatory response that leads to destruction of the tooth supporting structures. Consequences of periodontitis include tooth mobility and eventually tooth loss. Severe periodontitis, threatening tooth retention, affects approximately 10% of UK adults; while moderate periodontitis affects 40-60% (Morris *et al.*, 2011). A recent estimate calculated that 4.4 million adults in the UK were suffering from severe periodontitis (Griffiths and Preshaw, 2014).

Periodontal diseases are currently classified into eight categories as detailed in

Figure 1.2. This classification system was developed at an international workshop in 1999 (Armitage, 1999) and has been used extensively since. The two main categories relevant to this study are chronic and aggressive periodontitis. Chronic periodontitis has several principal clinical features or characteristics: most prevalent in adults; destruction consistent with presence of local factors; subgingival calculus is often present; variable microbiota; slow-moderate rate of progression; it can be exacerbated by systemic diseases, cigarette smoking or emotional stress (Lindhe *et al.*, 1999). Chronic periodontitis can be further characterised by extent and severity. Extent of disease is categorised as localised or generalised, depending on the percentage of sites affected (30% cut off). Severity is categorised according to clinical attachment loss (CAL): slight = 1-2 mm CAL, moderate = 3-4 mm CAL, severe = ≥5 mm CAL. These two descriptors are added to the diagnosis to give the final diagnosis e.g. Severe generalised chronic periodontitis. Aggressive periodontitis has three primary features: individuals are systemically healthy, there is rapid attachment loss and bone destruction, and familial aggregation (Lang *et al.*, 1999). Secondary features comprise: microbial deposits being inconsistent with the severity of destruction, elevated proportions of *Actinobacillus actinomycetemcomitans* and *Porphyromonas gingivalis*, phagocyte abnormalities, hyper-responsive macrophage phenotypes and progression that may be self-arresting (Lang *et al.*, 1999). In practice, there are often cases in which it can be challenging to differentiate between severe chronic periodontitis and aggressive periodontitis.

Since the development of this classification system there has only been a minor update (American Academy of Periodontology, 2015). However, in 2017 an international workshop convened to develop a new classification system (Caton *et al.*, 2018). The results of this workshop have only recently been published and are not yet in routine use.

I	Gingival diseases
II	Chronic periodontitis
III	Aggressive periodontitis
IV	Periodontitis as a manifestation of systemic disease
V	Necrotising periodontal disease
VI	Abscesses of the periodontium
VII	Periodontitis associated with endodontic lesions
VIII	Developmental or acquired deformities and conditions

Figure 1.2 Main disease categories in the 1999 periodontal disease classification system.

1.2.2 *Risk factors for periodontal diseases*

Periodontal disease is predominately related to the dental plaque biofilm. The individual's response to this microbial challenge is the major factor in disease susceptibility, severity and progression. Several risk factors have been identified and confirmed as important through several decades of research (Genco and Borgnakke, 2013). A number of national databases made the study of risk factors possible. For example, the National Health and Nutrition Examination Survey (NHANES) has reported on risk profiles for periodontitis in US adults (Dye *et al.*, 2007; Eke *et al.*, 2016). Broadly, risk factors can be classified as systemic or local, depending on their mode of action. Furthermore, risk factors can be sub-divided into those which are modifiable or non-modifiable, a useful distinction for patients and dental professionals. Figure 1.3 details the known risk factors for periodontal disease using this categorisation.

	Risk Factors		
	Modifiable factors		**Non-modifiable factors**
Local factors	Acquired	Anatomical	
	Plaque & calculus Partial dentures Open contacts Overhanging & poorly contoured restorations	Malpositioned teeth Furcations Root grooves & concavities Enamel pearls	
Systemic factors	Smoking Diabetes Poor diet Certain medications Stress		Socioeconomic status Genetics Adolescence Pregnancy Age Leukaemia
	Emerging evidence: Nutrition, Alcohol, Obesity/overweight		

Figure 1.3 Risk factors for periodontal diseases.

Adapted from the Good Practitioner's Guide to Periodontology (British Society of Periodontology, 2016)

Local risk factors

Given the significance of the microbial biofilm in periodontal pathogenesis, local factors which influence the amount of biofilm present are important. This is usually mediated by factors which impede biofilm removal through natural (saliva flow) or artificial means (oral hygiene procedures). Several anatomical variations can lead to increased biofilm development e.g. malpositioned teeth, furcations or uneven tooth surfaces. Several acquired local factors can also lead to increased biofilm accumulation. For example, plaque/calculus deposits, overhanging and poorly contoured restorations can make oral hygiene procedures more challenging and less effective. Partial dentures increase plaque deposition in both the adjacent teeth and opposing arch (Addy and Bates, 1979). Open contacts between teeth lead to increased food packing and hygiene difficulties. The influence of most of these factors can be reduced by remedial dental treatment (e.g. corrections of deficient restorations or closing contact points) or by educating patients about oral hygiene measures. The management of local risk factors is an essential component of successful periodontal therapy.

Tobacco smoking

Tobacco smoking is arguably the most important known risk factor for periodontitis. The first study associating tobacco smoking with periodontal disease was in 1947 and this exposure-risk relationship has subsequently been the subject of extensive investigation (Pindborg, 1947). Initially, the association was attributed to the poorer oral hygiene seen in smokers compared to non-smokers. However, subsequent studies with adjustment for confounders (including oral hygiene) concluded that moderate tobacco smoking is of itself a risk factor for periodontitis with odds ratios of 4-5 presented and a clear dose-response relationship observed (Grossi *et al.*, 1994; Grossi *et al.*, 1995). Furthermore, reviews of the topic have reinforced the importance of tobacco smoking as an independent risk factor (Bergstrom and Preber, 1994; Papapanou, 1996; Tonetti, 1998; Genco and Borgnakke, 2013; Leite *et al.*, 2018). Genco and Borgnakke (2013) provided five supporting factors for this: 1) consistency of results across many studies; 2) strength of the association; 3) dose-response of the association; 4) temporal sequence of smoking and periodontal disease; and 5) biological plausibility.

Analysis of the NHANES data collected between 1988-1994 estimated that over 50% of all cases of chronic periodontitis were attributed to cigarette smoking (Tomar and Asma, 2000). Extrapolating this to the UK population would equate to approximately 2.2 million individuals. Increased tooth loss in smokers has been consistently observed in many populations around the world including the United States of America (USA) (Albandar *et al.*, 2000; Krall *et al.*, 2006), Australia (Arora *et al.*, 2010), Brazil (Haas *et al.*, 2012) and

Thailand (Torrungruang *et al.*, 2012). Tobacco smoking has impacts on initial treatment outcomes (see section 1.2.7) as well as during longer-term periodontal maintenance with smokers being five times more likely to suffer from tooth loss (Chambrone *et al.*, 2010).

Diabetes

Diabetes is a metabolic disorder characterised by hyperglycaemia caused by defects in insulin action or production. Poorly controlled diabetes (type 1 or 2) is a risk factor for periodontal diseases with hyperglycaemia leading to adverse periodontal outcomes (Chapple and Genco, 2013). A two-way relationship has been described with poorly controlled periodontal disease also leading to poorer glycaemic control (Preshaw *et al.*, 2012; Chapple and Genco, 2013). Mechanical periodontal therapy has been shown to reduce HbA1c (a measure of hyperglycaemia) by 0.4% at 3 months post-treatment, which is equivalent to the addition of a second pharmacological drug (Preshaw *et al.*, 2012; Chapple and Genco, 2013). The combined effects of tobacco smoking and diabetes (i.e. the diabetic smoker) have been shown to be synergistic with regards to microbiological outcomes (Ganesan *et al.*, 2017b), although not confirmed by the limited clinical data available (Han *et al.*, 2012).

Other systemic factors

A number of other systemic factors have been categorised as risk factors for periodontitis, comprising: stress, poor diet and certain medications, with emerging evidence for the implication of nutrition, alcohol consumption and obesity. Stress, including distress and coping skills, as a risk factor is likely to act through several possible mechanisms including immunosuppression and modified behaviours (Genco and Borgnakke, 2013). A two-year study found those with active coping modes had improved periodontal outcomes compared to those with passive coping strategies (Wimmer *et al.*, 2005). Regarding obesity, several systematic reviews have shown a significant association with periodontal disease (Suvan *et al.*, 2011; Keller *et al.*, 2015; Gerber *et al.*, 2016) with one reporting an odds ratio (OR) of 2.13 for an association between overweight/obesity and periodontitis (Suvan *et al.*, 2011).

1.2.3 ***Clinical effects of tobacco smoking***

Smokers are at increased risk of a broad range of intra-oral effects. The most significant, at an individual level, is oral cancer; there is a strong synergistic relationship with alcohol consumption. At the most extreme, those who are heavy tobacco smokers (>40 cigarettes/day for >20 years) and heavy alcohol drinkers (>30 drinks/week) are at thirty-eight times increased risk of developing oral cancer (Blot, 1992). More recent data continues to show the importance of smoking and alcohol as risk factors, irrespective of human papillomavirus infection status, a relatively recently identified risk factor (Anantharaman *et al.*, 2016). Once

diagnosed, smokers have poorer survival rates compared to never- and former-smokers (Abrahao *et al.*, 2018).

Oral cancer is associated with significant morbidity and mortality. Although periodontitis is not directly life threatening it is likely to be a more significant consequence of tobacco smoking at a public health level. Periodontitis has a high global burden, being responsible for 3.5 million years lived with disability, $54 billion/year in lost productivity and a major portion of the $442 billion/year costs for oral diseases (Tonetti *et al.*, 2017). As previously discussed (see section 1.2.2) there are multiple risk factors for periodontitis, but tobacco smoking is arguably the most important and certainly the most significant environmental risk factor. Tobacco smoking is thought to affect the periodontal tissues via multiple pathways, such as effects on the host immune and inflammatory response and on the oral microbiome (see sections 1.2.4 and 1.2.5) (Palmer *et al.*, 2005).

Tobacco smokers also experienced other effects of smoking on their soft tissues including increased prevalence of mucosal disease such as melanosis (Hedin, 1977) and candidosis (Soysa and Ellepola, 2005). Similarly, tobacco smokers have poorer wound healing and are more likely to suffer complications after surgery e.g. 'dry sockets' after tooth extractions. Dental implants are also affected by tobacco smoking, with both short- and long-term effects. In the short term, tobacco smokers are at increased risk of failure of osseointegration (Hinode *et al.*, 2006). In the longer term, tobacco smokers are at increased risk of implant failure (Strietzel *et al.*, 2007; Chambrone *et al.*, 2014) and peri-implantitis (Heitz-Mayfield, 2008; Lindhe and Meyle, 2008; Sgolastra *et al.*, 2015) although the evidence is not yet convincing.

Finally, tobacco smokers have higher rates of dental staining and halitosis (bad breath). Although these may not be significant health impacts, they are often the most important to smokers in their impact on quality of life and can be useful prompts in cessation interventions.

1.2.4 *Microbiological effects of tobacco smoking*

Tobacco smoke has effects on the oral microbial ecology. It has been known for some time that tobacco smokers harbour greater numbers of potential periodontal pathogens than non-smokers (Palmer *et al.*, 2005). Recent profiling of microbial communities, using next generation sequencing, has demonstrated smokers to have significantly different periodontal microbiomes than non-smokers with a highly diverse, pathogen-rich, commensal-poor, anaerobic microbiome, suggesting that they are primed for future disease progression (Mason *et al.*, 2015; Wu *et al.*, 2016). Delima *et al.* (2010) demonstrated that, when smokers quit, they developed increased bacterial diversity and altered community composition with greater

numbers of health-associated species and significantly lower prevalence and abundance of periodontal pathogens. Conversely, Nociti *et al.* (2015) discuss that several studies have shown minor or no differences between smokers and non-smokers. These conflicting findings are perhaps due to the differences in microbiological techniques used in different studies.

1.2.5 *Vascular, immune and inflammatory effects of tobacco smoking*

Reaction to the plaque biofilm via immune and inflammatory responses are critical factors in individual susceptibility to periodontitis. Tobacco smokers experience impairment of the periodontal vasculature with lower oxygen tension (Hanioka *et al.*, 2000) and suppression of the normal inflammatory response to subgingival biofilm (which presents clinically as reduced gingival redness), volume of gingival crevicular fluid (GCF) and bleeding (Preber and Bergstrom, 1986; Lie *et al.*, 1998). When smokers quit, the local inflammatory response recovers quickly and they often experience a transient increase in gingival bleeding (Nair *et al.*, 2003). Tobacco smoking additionally reduces the healing potential of the tissues, negatively impacting on fibroblast function and collagen synthesis (Palmer *et al.*, 2005; Reuther and Brennan, 2014).

Neutrophils are critical cells in the maintenance of periodontal health and it is clear that tobacco smoke affects multiple functions of neutrophils that collectively contribute towards the tissue destruction seen in periodontitis (Palmer *et al.*, 2005). Tobacco smokers have increased numbers of T-cells and elevated T-cell responsiveness leading to greater potential for periodontal breakdown (Loos Bruno *et al.*, 2004). Additionally, it has been suggested that an imbalance in cytokine production seen in smokers affects periodontal pathogenesis (Genco and Borgnakke, 2013).

1.2.6 *Nicotine effects on the oral tissues*

Whole tobacco smoke contains a complex mixture of an estimated 10,000-100,000 chemicals (Rodgman and Perfetti, 2009), including over 70 known human carcinogens (Smith *et al.*, 1997; Smith *et al.*, 2000; Smith *et al.*, 2001) and several other notable compounds including: nicotine, hydrogen cyanide, formaldehyde, lead, arsenic, ammonia, benzene, carbon monoxide, nitrosamines and polycyclic aromatic hydrocarbons (Talhout *et al.*, 2011).

As previously discussed (see section 1.2.3) whole tobacco smoke has detrimental effects on oral and periodontal tissues and *in vitro* studies have shown it to be highly toxic to oral cells (Zhang *et al.*, 2009) with significant disruption to cellular functions (Semlali *et al.*, 2011). However, it is largely unknown which compounds in tobacco smoke are responsible for the observed effects, as most studies evaluate the impact of whole cigarette smoke rather than a

particular component. Often studies and review papers confuse nicotine and whole tobacco smoke, using the terms interchangeably. For example, within their review, Genco and Borgnakke (2013) postulate that the smoking effects seen on periodontal health are 'mainly through the effects of nicotine' and that nicotine enhances the degranulation of neutrophils, making them more sensitive to bacterial challenge. In support of this argument, they cite a clinical study (Söder *et al.*, 1999) which investigated smokers but did not include nicotine as a variable (whole tobacco smoking was compared to not smoking). Nicotine and whole tobacco smoke have been confused in this instance (although not by Söder *et al.* (1999), who do not mention nicotine once within their paper). Javed *et al.* (2017b) made similar errors in their review which we highlighted in journal correspondence (Holliday *et al.*, 2017b).

The specific pathogenic role of nicotine has been of increasing relevance with the introduction and widespread use of NRT and recent development of novel nicotine products such as e-cigarettes. A review concluded that nicotine has likely been 'unfairly blamed' for the detrimental oral effects of tobacco smoke (Palmer *et al.*, 2005). There have been a large number of *in vitro* studies investigating the effect of nicotine in isolation on oral and periodontal cells. These have often reported contradictory results. For example Wu *et al.* (2013), stated that 'nicotine, the main toxic component in tobacco, was confirmed as the main effect of smoking on periodontal tissue destruction' whereas Checchi *et al.* (1999), concluded 'nicotine by itself is toxic only at concentrations higher than that found in plasma and crevicular fluid of heavy smokers'. Wyganowska-Swiatkowska and Nohawica (2015) published a 'systematic review' on the topic and concluded that exposing periodontal fibroblasts to nicotine resulted in detrimental effects on viability and cellular functions. However, the review methodology and reporting fell significantly below conventional standards (e.g. the Preferred Reporting Items for Systematic Reviews and Meta-Analyses [PRISMA]) and the paper would be best described as a narrative non-systematic review. Hence, a robust systematic review has not yet been published on this important topic and researchers and dental professionals are left with an unclear message about the oral health harms from nicotine. Undoubtedly, this has contributed to some of the perceptions around nicotine as discussed later (see section 1.4.7). One of the objectives of this thesis is therefore to conduct a systematic review on this topic.

A number of animal studies have reported detrimental periodontal and healing effects of nicotine administration (Nociti *et al.*, 2000; Nociti *et al.*, 2001; Pinto *et al.*, 2002; Cesar-Neto *et al.*, 2005; Francisco *et al.*, 2007; de Almeida *et al.*, 2011). They used rat models with ligatures around teeth to stimulate periodontal disease and once daily intraperitoneal

injections of various nicotine concentrations. They generally concluded that administration of nicotine did not produce periodontal bone loss by itself but did seem to enhance existing inflammation (Nociti *et al.*, 2015). The clinical relevance of these studies to humans is challenging to interpret, particularly given the difference in the mode of nicotine administration and dosing compared to smoking. Further studies, using passive smoking models, reported that rats exposed to cigarette smoke had higher ligature-induced bone loss and other detrimental effects but nicotine itself was not a variable (César *et al.*, 2004; Braga *et al.*, 2005; Cesar-Neto *et al.*, 2005; Batista *et al.*, 2006).

It is well known that tobacco smokers have significant impairment of the periodontal vasculature, although the specific role of nicotine in this is unclear. On one hand, nicotine activates the sympathetic nervous system to cause generalised vasoconstriction (Toshiya *et al.*, 2004). Conversely, nicotine applied topically can have angiogenic effects and has been shown to increase blood flow and oxygen tension in the gingival tissues (Johnson *et al.*, 1991; Sorensen, 2012). Nicotine administered via transdermal patches has even been suggested to have a therapeutic effect with reduced myocardial ischaemia (Mahmarian *et al.*, 1997) and facilitation of wound healing after surgery (Jacobi *et al.*, 2002; Reuther and Brennan, 2014).

The oral health effects of nicotine have been investigated to some extent through clinical studies of NRT. Christen *et al.* (1985) compared nicotine-containing and placebo chewing gum, concluding there was no significant influence on oral health parameters. Another study investigated nicotine chewing gum compared to a nicotine sublingual tablet, comparing tooth staining (Whelton *et al.*, 2012). They concluded that using nicotine chewing gum for 6 weeks in a smoking cessation programme resulted in reduced stain and shade lightening, with no adverse events in either group. Conversely, a meta-analysis of hundreds of studies cited oral soreness or ulcers as adverse events of orally-administered NRT (Mills *et al.*, 2010; Stead *et al.*, 2012). Analysis is complicated because these effects are often seen in smoking cessation with mouth ulcers reported in about 40% of individuals who successfully quit, usually within the first two weeks (McRobbie *et al.*, 2004). However, Mills *et al.* (2010) accounted for this by comparing to inert controls (e.g. placebo) and reported that orally-administered NRT was associated with mouth and throat soreness (5.4% prevalence, OR 1.87, 95% CI: 1.36-2.57) and mouth ulcers (OR 1.49, 95% CI 1.05-2.20) (Mills *et al.*, 2010). They advise that users who develop oral symptoms should switch to an alternative form of delivery e.g. skin patch or nasal spray.

Finally, nicotine metabolites, particularly cotinine, could be of importance, given its extended half-life. No clinical studies exist but *in vitro* studies have found that cotinine exposure did

not result in statistically significant effects on the periodontal ligament (PDL) fibroblasts (James *et al.*, 1999). This corroborates the results of other studies which showed cotinine to have lower toxicity than nicotine (Babich and Borenfreund, 1992). However, the relatively long half-life of cotinine will expose cells to its effects for an extended period, potentially escalating any impacts.

In summary, nicotine appears not to be a major pathological agent in tobacco smoke, although it may have some effects. There are numerous *in vitro* studies on oral cells, which would benefit from being collated in a systematic review, one of the objectives of this thesis.

1.2.7 ***Impact on periodontal treatment outcomes***

A common scenario that presents to dental professionals is that of an individual who has periodontitis and who has smoked tobacco for many years. In this case, the focus moves away from the impact of tobacco smoking on aetiology and pathogenesis, towards treatment outcomes. Given the known damaging effect of smoke on periodontal tissues, the logical corollary is that periodontal treatment outcomes will be worse in smokers and better in non-smokers with former smokers having intermediate responses (Heasman *et al.*, 2006).

Studies have shown that tobacco smokers have poorer responses to both non-surgical and surgical periodontal therapies (Papantonopoulos, 2004; Heasman *et al.*, 2006; Johnson and Guthmiller, 2007; Brurberg *et al.*, 2008; Chambrone *et al.*, 2009; Preshaw *et al.*, 2013; Nociti *et al.*, 2015; Leite *et al.*, 2018). A review (Brurberg *et al.*, 2008) found that 34 of 38 studies showed poorer responses to periodontal therapies in smokers compared to non-smokers with a mean difference in post-therapeutic pocket probing depths (PPDs) being 0.33 mm (95% CI 0.22-0.42 mm) (Brurberg *et al.*, 2008) which is of questionable clinical significance. More clinically significant PPD reductions (around 1 mm) have been reported in individual studies (Jin *et al.*, 2000). Not all studies, however, demonstrated improved clinical outcomes in non-smokers (Pucher *et al.*, 1997; Zuabi *et al.*, 1999). For example, Pucher *et al.* (1997) reported that smokers and non-smokers responded similarly to non-surgical periodontal therapy after nine months.

Two prospective studies (Preshaw *et al.*, 2005; Rosa *et al.*, 2011) have investigated the impact of quitting smoking during periodontal therapy. A systematic review and meta-analysis (Chambrone *et al.*, 2013) concluded that there was a statistically significant beneficial impact of quitting smoking on the number of sites demonstrating PPD reductions ≥ 2 mm (incident rate ratio: 1.30, 95% CI: 1.17-1.44). A 2 mm or greater reduction in PPD is generally regarded as clinically meaningful at an individual site (Greenstein, 2003). Indeed, it has been suggested

that for smokers with periodontitis, dentists should focus on smoking cessation as a primary treatment strategy for the periodontitis, rather than conventional therapies (Preshaw *et al.*, 2018).

Following an active course of periodontal therapy, individuals should be entered into a supportive periodontal therapy (SPT) phase of treatment, sometimes also known as periodontal maintenance (Cohen, 2003; British Society of Periodontology, 2016). Maintaining smoking abstinence or encouraging smoking cessation are critical aspects of this phase of treatment. Studies (McGuire and Nunn, 1996a; McGuire and Nunn, 1996b; Preshaw and Heasman, 2005; Dannewitz *et al.*, 2016) have repeatedly demonstrated that smokers have poorer outcomes during this phase with one study (Chambrone *et al.*, 2010) calculating that smokers were five times more likely to suffer from tooth loss. Risk assessment tools are often used during SPT to customise the frequency and content of SPT visits (Lang *et al.*, 2015). The Periodontal Risk Assessment (PRA) developed by Lang and Tonetti (2003) assesses risk in six domains and is available for online use from the University of Bern (Ramseier, 2009). One of these domains is tobacco smoking and the PRA places individuals into five categories: non-smoker, former smoker (those who quit more than five years ago), occasional smoker (< 10 cigarettes/day), smoker (10-19 cigarettes/day) and heavy smoker (≥20 cigarettes/day). Non-smokers and former smokers are deemed to have a low risk of recurrence of periodontitis, while occasional smokers and smokers are deemed to have moderate risk, and heavy smokers high risk. This categorisation is now outdated and can be difficult to use. For example, an individual who quit smoking 0-5 years ago does not easily fit into any category and the category name of 'occasional smoker' is misleading given this category includes those who smoke up to 10 cigarettes/day. Another risk assessment tool is the Periodontal Risk Calculator (PRC) which has a more detailed categorisation of smoking habits, detailing what is smoked and how often (Oral Health Innovations Ltd, 2008). However, the algorithm for how this relates to the risk score is not available as this is a commercial product.

In summary, tobacco smoking is a risk factor for both periodontal disease development and treatment outcomes. Hence, supporting patients to quit smoking is an important aspect of disease prevention and an essential component of successful periodontal therapies. The next section (1.3) will discuss smoking cessation generally and within the dental context.

1.3 **Smoking cessation**

1.3.1 ***The development of smoking cessation***

The twentieth century's smoking epidemic peaked in the middle of the century with over 80% of males smoking in 1948 (Royal College of Physicians, 2000). Since the 1960s there has been a steady decline in smoking prevalence rates. Landmark reports (The Royal College of Physicians, 1962; Surgeon General, 1964) linking smoking to diseases such as lung cancer were fundamental in helping this decline. Likewise, the World Health Organisation (WHO) Framework Convention on Tobacco Control (FCTC) developed during the first few years of the 21st century, have contributed to the continued decline seen worldwide (World Health Organisation, 2008; Ng *et al.*, 2014; Bilano *et al.*, 2015). The FCTC was accompanied by the MPOWER framework to identify key elements for implementation of the treaty alongside the Articles contained within the FCTC. The MPOWER framework comprises: monitoring tobacco use and prevention policies, protecting people from tobacco, offering help to quit tobacco use, enforcing bans on tobacco advertising, promotion and sponsorship, and raising taxes on tobacco (World Health Organisation, 2008).

A key component of tobacco control policies is the offer of smoking cessation support to smokers, included in Article 14 of the FCTC. During the 1990s within the UK, government policies and guidelines were developed for smoking cessation support, including by healthcare professionals (Department of Health, 1998; Raw *et al.*, 1998; Raw *et al.*, 1999). Dedicated stop smoking services were developed nationwide by 2000 with subsequent evaluations and reviews showing the success of the service (Bauld *et al.*, 2010; Dobbie *et al.*, 2015). The key features of these services included access to behavioural support (either one-to-one or group sessions) and pharmacotherapy (such as NRT, varenicline, bupropion) (Dobbie *et al.*, 2015). Evaluations of the services found that those attending the stop smoking services are 3-4 times more likely to quit than those attempting to do so by willpower alone (Dobbie *et al.*, 2015). Historically, however, relatively few smokers access these services: around 6-10% but with a recent decline to 4% in May 2016 (West and Brown, 2016). Many barriers have been reported to smokers accessing these services including: fear of failure; fear of being judged; lack of knowledge; access barriers e.g. childcare issues; and perceptions about pharmacotherapy cost and ineffectiveness (Roddy *et al.*, 2006a; Murray *et al.*, 2009). Recent declines in client numbers have been attributed to: funding cuts; service reorganisation (particularly in England where services moved from the National Health Service [NHS] to local authorities); lack of mass media campaigns to promote the services; and smokers preferring to use e-cigarettes (Smith *et al.*, 2018).

Current national guidelines continue to require that all smokers attending healthcare services are advised and encouraged to stop and given the support they need (The National Institute for Health and Care Excellence, 2018). Unfortunately, the current austerity programme has limited access to services with a recent survey reporting successive budget cuts during 2015 – 2017, with only 61% of the English local authorities providing a specialist stop smoking service to all smokers in 2017 (Cancer Research UK and Action on Smoking and Health, 2018). In our local area (North East England), although there have been recent changes, Newcastle upon Tyne still has a specialist stop smoking service operated by Change Grow Live (Change Grow Live, 2018). Surrounding areas have a mixture of services available.

Not all experts agree on the need for services to help smokers quit, with a recent paper arguing that unassisted quit attempts were undervalued (Chapman and Wakefield, 2013). The authors specifically challenged the need for nicotine products, referring to the successes in the era prior to their availability. They cited the American Cancer Society who estimated that 90% of the 37 million Americans who stopped smoking since the 1964 Surgeon General's report had done so unaided (American Cancer Society, 1986). However, for countries at the end of the tobacco epidemic (i.e. stage IV) (Lopez *et al.*, 1994), many feel there is an important role for the specialist stop smoking services in supporting those remaining smokers to quit. The 'hardening' hypothesis states that remaining smokers are 'hard-core' smokers and find it more difficult to quit. This hypothesis has an intuitive and common-sense appeal; nonetheless, although it is supported by some evidence (Shiffman *et al.*, 2008), it is not strongly supported in the literature (Hughes, 2011; Cohen *et al.*, 2012; Docherty and McNeill, 2012).

Finally, in some nations, harm reduction approaches have been used alongside other tobacco control measures consistent with the MPOWER framework and the FCTC. In the UK, national guidance recommends harm reduction approaches for those not able or wanting to fully quit, those not wanting to quit nicotine, or those who aren't ready to quit but want to reduce the amount they smoke (The National Institute for Health and Care Excellence, 2013b). The rationale for this approach is two-fold. Firstly, reduction may eventually lead to complete cessation with smokers who cut down being more likely to attempt and be successful in quitting ('cutting down to quit'). Secondly, there are some benefits to reducing smoking, although these are limited; complete cessation should be the ultimate objective of gradual reduction, as the National Institute of Clinical Excellence (NICE) harm reduction guidance explains (The National Institute for Health and Care Excellence, 2013b). All three major fatal smoking-related diseases (coronary heart disease, lung cancer and COPD) have a

clear dose-response relationship between tobacco consumption and risk of developing or dying from the disease (Forey *et al.*, 2011; Lee *et al.*, 2012). Reducing the exposure to tobacco toxins is likely to lead to a reduction in disease burden, especially for diseases such as COPD with a steep dose-response relationship (Begh *et al.*, 2015). However, it must be emphasised that the evidence is mixed and a recent meta-analysis of coronary heart disease and stroke concluded that smoking only one cigarette per day carried a large risk, about half that of a twenty per day smoker (Hackshaw *et al.*, 2018). There are four main harm reduction approaches: stopping smoking but using a nicotine-containing product to prevent relapse, cutting down prior to stopping smoking, smoking reduction (with or without a nicotine-containing product) and temporary abstinence from smoking (with or without a nicotine-containing product)(The National Institute for Health and Care Excellence, 2013b). Within the context of this thesis harm reduction relates to smoking reduction i.e. reduction in cigarettes per day.

1.3.2 *Smoking cessation delivery by healthcare professionals*

Within the UK, national guidance recommends that all patients should be asked if they smoke by their healthcare professionals (HCPs). If they are smokers, they should be offered advice on how to stop and a referral made to an evidence-based smoking cessation service (The National Institute for Health and Care Excellence, 2013a). HCPs such as medical doctors and dentists, can provide smoking cessation advice in many different formats. The most frequently recommended format is that of a 'Very Brief Advice' (VBA) intervention which is designed to last 30 seconds and usually follows a Three A's format: Ask, Advise, Act. The patient should be asked about smoking and have their smoking status recorded in their records. They should be advised that the best way to quit is though using behavioural support plus medication. The HCP should then act on the patient's response by: referring to a specialist stop smoking service and/or prescribing pharmacotherapy or agreeing to review at subsequent visits if the patient is not interested at the present time (National Centre for Smoking Cessation and Training, 2012c). There are conflicting instructions between different guidance documents regarding the 'Advise' step. Some guidance recommends that if the intervention is designed to have a 30 second duration, it should not mention any harms of smoking/personal benefits of quitting in order to avoid entering into a prolonged discussion and for fear of producing a defensive reaction and anxiety in the patient (Aveyard *et al.*, 2012; National Centre for Smoking Cessation and Training, 2012c). Other guidance suggests that the personal benefits of quitting should be discussed with patients during the brief intervention; in these circumstances, it is likely that the duration of the intervention will need

to be several minutes to allow sufficient dialogue around this aspect (National Centre for Smoking Cessation and Training; Public Health England, 2014b; The National Institute for Health and Care Excellence, 2018). Occasionally a Five A's technique is recommended: Ask the patient about their tobacco usage, Advise them to quit, Assess their willingness to quit, Assist them in quitting, and Arrange follow-ups (Action on Smoking and Health, 2012; British Dental Association, 2015).

A Cochrane systematic review (Stead *et al.*, 2013a) looked at the effect of a brief advice intervention delivered by physicians. Data from 17 studies were pooled and brief intervention was shown to be effective compared to no advice (Relative Risk [RR]: 1.66, 95% CI: 1.42-1.94). More intensive interventions gave a higher estimated effect (RR 1.84, 95% CI:1.60-2.13) but, statistically, there was no difference between minimum and intensive interventions (Stead *et al.*, 2013a). Assuming an unassisted 6-month success rate of 3%, a brief advice intervention can increase the quit rates (6-month) to 5% (Stead *et al.*, 2013a).

Despite brief interventions being designed to be quick and simple to deliver, the rates of delivery to patients appear suboptimal. Self-reported data for medical primary care settings (general medical practitioners [GMPs]) suggest that almost all new patients are asked about their smoking status, but with far fewer regular patients being asked or routinely being advised to quit (Stead *et al.*, 2009). English data reported 98% of new patients had smoking status recorded while only 63% of returning smokers had their status checked and updated (McEwen *et al.*, 2005). A recent audit completed in secondary care reported that, for hospital patients, fewer than a quarter of patients were asked if they smoked and only a quarter of smokers were asked if they would like to quit smoking (British Thoracic Society, 2016). Barriers to and facilitators of physicians' engagement with smoking cessation have been extensively studied. For example, Stead *et al.* (2009) conducted a large European review of general practitioners that identified several factors: patient characteristics (smoking-related symptoms, pregnancy, heavy smokers), physician characteristics (own smoking status, attitude and cessation-specific knowledge and skills), and structural factors (reimbursement and time required).

1.3.3 *Behavioural support for smoking cessation*

Behavioural methods of support form an important component of stop smoking services and take several formats. A series of Cochrane systematic reviews have evaluated many of these interventions (Stead *et al.*, 2013a; Stead *et al.*, 2013b; Whittaker *et al.*, 2016; Lancaster and Stead, 2017; Stead *et al.*, 2017; Taylor *et al.*, 2017).

Individual behavioural support

Individual behavioural support involves face-to-face meetings with a trained smoking cessation counsellor. It typically involves weekly sessions over a period of four to eight weeks. There is high quality evidence that individual counselling is more effective than a minimal behavioural intervention (e.g. brief advice), when pharmacotherapy (NRT) is not offered to participants (RR 1.57, 95% CI: 1.40-1.77) (Lancaster and Stead, 2017). However, individual behavioural support is often combined with pharmacotherapy and there is moderate quality (downgraded due to imprecision) evidence that it is also effective in this circumstance (RR 1.24, 95% CI: 1.09-1.53) (Lancaster and Stead, 2017).

Group behavioural support

Group behavioural support involves meetings in which smokers receive information, advice and encouragement and some form of behavioural intervention. Sessions are typically weekly over a period of four weeks. There is moderate quality evidence (most studies at risk of bias) that group programmes are more effective than a self-help programme (RR 1.88, 95% CI: 1.52-2.33) (Stead *et al.*, 2017). There is low quality evidence (low grading due to inconsistency and risk of bias) for effectiveness compared to a brief intervention from a health care provider (RR 1.22, 95% CI: 1.03-1.43) and compared to no-intervention controls (RR 2.60, 95% CI 1.80-3.76) (Stead *et al.*, 2017). There is no evidence for effectiveness of a group programme plus pharmacotherapy compared with pharmacotherapy alone (RR 1.11, 95% CI: 0.93-1.33) (Stead *et al.*, 2017).

Internet-based interventions

The internet is a potentially powerful platform to provide cessation support with over 3.5 billion users (smokers and non-smokers) worldwide in 2016. Studies suggest interactive and tailored internet-based interventions are effective compared to a non-active control (RR 1.15, 95% CI: 1.01-1.30, low quality evidence) or moderately effective when combined with behavioural support (RR 1.69, 95% CI: 1.30-2.18, moderate quality evidence) (Taylor *et al.*, 2017). These results should be interpreted with caution as the evidence was often at high risk of bias with substantial statistical heterogeneity (Taylor *et al.*, 2017).

Telephone counselling and mobile phone-based interventions

Telephone counselling can supplement or be a substitute for face-to-face contact and can be used alongside pharmacotherapy. There are financial and logistical advantages to providing support by telephone. The counselling can be proactive (counsellor initiates the calls) or reactive (on demand service for users to initiate). These helplines or quitlines are extensively used in countries without free-at-the-point-of-service, face-to-face cessation services as in the

UK. This is highlighted by the location of research studies, with sixty being completed in North America compared to three in the UK (Stead *et al.*, 2013b). Both proactive and reactive forms of counselling have been shown to be effective (Stead *et al.*, 2013b). For proactive forms there is a dose-response relationship with three or more calls being superior to fewer (Stead *et al.*, 2013b). Mobile phone-based interventions, such as text messaging services, have also been shown to be effective (Whittaker *et al.*, 2016).

1.3.4 *Pharmacotherapy for smoking cessation*

A number of pharmacological methods are available for smoking cessation. They can be used alone or alongside behavioural support. Often they are available over-the-counter or on prescription from a healthcare provider (or both) depending on local arrangements. A broad range of medications have been used as cessation aids, with most evidence for NRT, bupropion (Zyban), varenicline (Champix) and, to a lesser extent, cytisine.

NRT is available in many different forms (patches, chewing gum, lozenges, sublingual tablets, sprays and inhalers) and aims to reduce motivation to smoke and the physiological and psychological withdrawal symptoms experienced during a quit attempt. Within the UK, over-the-counter NRT was, by far, the most popular quitting aid prior to 2013, after which e-cigarettes became the most used (West *et al.*, 2018). Varenicline is a selective nicotinic receptor partial agonist and is a prescription-only treatment. The use of varenicline peaked in 2012 with 11% of smokers using it during quit attempts, with a steady decline since to around 2-4% in 2017/2018 (West *et al.*, 2018). Buproprion is now scarcely used, with the number of courses dispensed in the England seeing a 15-fold decrease between 2001 and 2014 (Department of Health, 2015). Cytisine is not available in the UK but is commonly used in Poland and other parts of Eastern Europe (Walker *et al.*, 2016).

A Cochrane overview of reviews and network meta-analysis included 267 studies involving over 100,000 participants (Cahill *et al.*, 2013). It concluded that NRT, bupropion, varenicline and cytisine increased the chances of quitting with odd ratios in the 2-4 region (Cahill *et al.*, 2013). Combination NRT (i.e. two NRT products, a slow and fast release) and varenicline were equally effective quitting aids (Cahill *et al.*, 2013). None of the treatments had adverse events that would militate against their use (Cahill *et al.*, 2013). The authors of this review also concluded that no further research was warranted into the efficacy or safety of NRT due to the large number of studies already conducted, with future trials unlikely to modify what was known about benefits and risks of the treatment (Cahill *et al.*, 2013).

1.3.5 ***Smoking cessation interventions by dental professionals***

Guidance documents

Dental professionals, in a similar fashion to other HCPs, are advised to provide brief advice interventions to their patients who smoke. A range of national guidance documents are available for dental professionals as detailed in Table 1.1.

Guidance document	Publisher and year	Content
Smoking: brief interventions and referrals (PH1)	The National Institute for Health and Care Excellence (2018)	Advises that everyone who smokes should be advised to quit. If an individual presents with a smoking-related disease, the cessation advice should be linked to their medical condition. Dentists should refer people who smoke to specialist services.
Stop smoking interventions and services (NG92)	The National Institute for Health and Care Excellence (2018)	At every opportunity, people should be asked if they smoke and advised to stop in a way that is sensitive to their preferences. VBA interventions should be delivered according to the National Centre for Smoking Cessation Training (NCSCT) training module (National Centre for Smoking Cessation and Training, 2012c). Smokers interested in quitting should be referred to a stop smoking service.
The Clinical Case for providing stop smoking support to Dental Patients	National Centre for Smoking Cessation and Training (2012a)	VBA intervention suggested: ASK and record smoking status ADVISE - on personal health benefits of stopping smoking ACT - prescribe, monitor, refer.
Very Brief Advice training module	National Centre for Smoking Cessation and Training (2012c)	This is an online training module for healthcare professionals. Describes a technique that allows an intervention to be delivered in <30 seconds. The 'advise' step deliberately leaves out the health benefits of stopping smoking/ harms of smoking in order to minimise the duration of the intervention and avoid a defensive reaction.
Tobacco and Oral Health	Action on Smoking and Health (2016)	Suggests dentists provide smoking cessation advice using the 3 A's technique as described by the NCSCT (National Centre for Smoking Cessation and Training, 2012c). The previous versions of this guidance recommended the 5 A's technique: Ask, Assess, Advice, Assist, Arrange (Action on Smoking and Health, 2012).
Smokefree and Smiling. Second edition.	Public Health England (2014b)	Tobacco users should receive a VBA intervention using the 3 A's technique. There is confusion within the document regarding the 'advise' step. It states 'advise on the

Guidance document	Publisher and year	Content
		personal benefits of quitting' but contradicts this later when recommending the NCSCT VBA approach.
Delivering better oral health: an evidence-based toolkit for prevention. Third Edition.	Public Health England (2014a)	VBA advised using 3 A's technique. Specifically recommends the NCSCT VBA training module (National Centre for Smoking Cessation and Training, 2012c).
Smoking cessation in NHS dentistry. BDA evidence summary.	British Dental Association (2015)	Concludes that behavioural interventions by health care professionals are effective in reducing tobacco use in smokers and smokeless tobacco users.

Table 1.1 Guidance documents for dental professionals providing smoking cessation interventions.

Evidence

A Cochrane systematic review (Carr and Ebbert, 2012) looked specifically at tobacco cessation within the dental setting and found it to significantly increase the odds of tobacco abstinence at 6 to 24 months (OR: 1.71, 95% CI: 1.44-2.03). However, there was high heterogeneity between studies ($I^2 = 61\%$), likely to be partially explained by the settings investigated. These varied from private specialist dental practices to federally funded general dental practices. Some studies targeted school children while others focused on adults, also contributing to the heterogeneity. A post hoc subgroup analysis of adult smokers in dental practice settings (5 studies) demonstrated no evidence of heterogeneity ($I^2 = 3\%$) and a significant benefit of the intervention (OR 2.38, 95% CI: 1.70 -3.35) as presented in Figure 1.4. As previously, assuming an unassisted 6-month success rate of 3%, an intervention in the dental setting could increase the quit rates (6-month) to 7%.

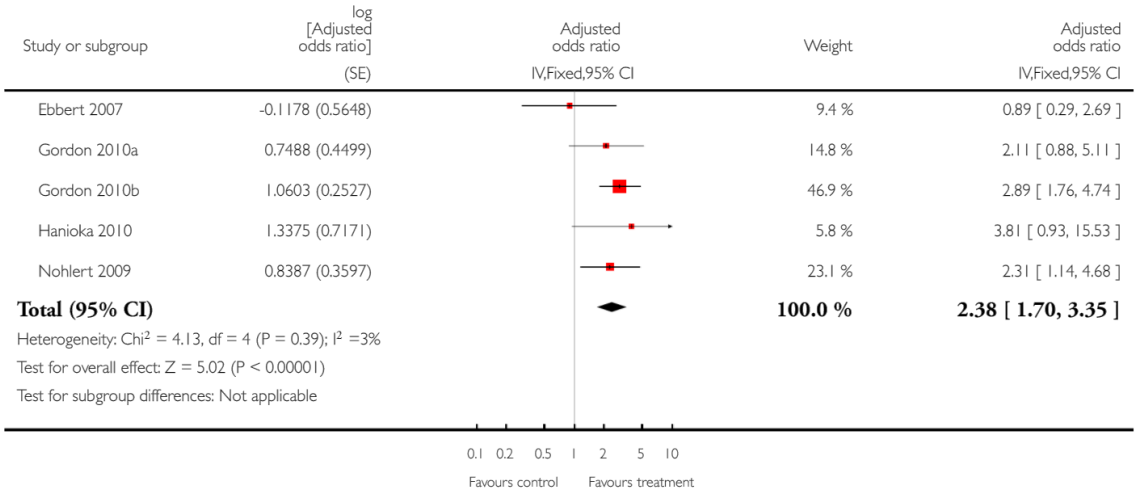

Figure 1.4 Smoking cessation following behavioural interventions by general dental practitioners.

Comparison: Behavioural interventions verses control. Outcome: Abstinence at the longest follow-up. Subgroup of trials in adult smokers seen by general dental practitioners. Reproduced from Carr and Ebbert (2012).

For patients suffering from periodontal disease, smoking cessation is especially important (see section 1.2.7), as highlighted in a number of European workshop consensus reports (Ramseier *et al.*, 2006; Ramseier *et al.*, 2010). Dental professionals are in a unique position to provide smoking cessation advice (SCA) as they often see patients over a sustained period of time for periodontal therapy, which has better outcomes when smokers quit (Chambrone *et al.*, 2013). Additionally, patients with periodontitis are likely to have several visible signs of the disease process (staining, recession, drifting, mobility, tooth loss) which can be useful prompts for quit attempts.

Both of the European workshop consensus reports identified that education in dental schools lacked both a knowledge-based curriculum and practical skills training of behaviourally-based interventions (Ramseier *et al.*, 2006; Ramseier *et al.*, 2010). A lack of training has often been identified as a barrier to providing SCA by dental professionals of all professional groups (Stacey *et al.*, 2006; Ahmed *et al.*, 2018). A European survey in 2009 reported that overall 67% (UK data: 100%) of dental schools included tobacco education in their curricula for dentists, but only 18% (UK data: 67%) included any practical aspect of education e.g. delivering smoking cessation interventions. Assessment rates were low, with only 27% (UK data: 89%) of dental schools assessing theoretical knowledge and 4% (UK data: 11%) assessing practical skills. An update of UK dental schools in 2016 reported an improved situation with practical assessment rates increasing to 72% (Holliday *et al.*, 2017a). All UK programmes expected their graduates to be clinically competent at discussing the health consequences of smoking, delivering a brief smoking cessation intervention and referring patients to stop smoking services (Holliday *et al.*, 2017a).

Harm reduction approaches

As previously discussed (see section 1.3.1), harm reduction approaches are advised for those not able or wanting to quit in one step (abruptly), in order to increase the likelihood of later quit attempts and reduce health harms (The National Institute for Health and Care Excellence, 2013b). From a periodontal disease perspective, harm reduction is also an important consideration with patients often asking if there is benefit for their gum health in cutting down. The damage caused by tobacco smoke does appear to be dose-dependent with disease severity increasing with a greater number of cigarettes smoked per day or increasing pack-years (Martinez-Canut *et al.*, 1995; Tomar and Asma, 2000; Dietrich *et al.*, 2015). Few studies have demonstrated a dose-response for treatment outcomes. A dose-response has been shown in one study for surgical outcomes (Cortellini and Tonetti Maurizio, 2015) and two studies for tooth loss during supportive periodontal therapy (Rieder *et al.*, 2004; Matuliene *et*

al., 2008). Chaffee *et al.* (2016) warned about compensatory smoking (e.g. deeper breaths to obtain as much nicotine as possible from each cigarette), with reduced smoking not necessarily leading to reduced exposure to harmful tobacco products. Therefore, the use of NRT while cutting down is critical for the harm reduction concept (The National Institute for Health and Care Excellence, 2013b) as it reduces the extent of compensatory smoking by providing an alternative nicotine source. In patients who continue to smoke, there has been some consideration of approaches that control the damage, slowing the disease process (Chaffee *et al.*, 2016). Host modulation therapies may reduce the damage caused by tobacco smoke. Such therapies include agents that reduce inflammatory response or promote healing after resolution of inflammation. There is some evidence that the use of tetracycline family antibiotics has positive effects for smokers when combined with periodontal debridement (Chaffee *et al.*, 2016), although not all studies agree (Needleman *et al.*, 2007).

In summary, dental professionals are in an influential position to provide effective SCA to their patients who smoke. Dental professionals are advised to deliver SCA using VBA interventions such as the 3 A's technique. Ideally, this will result in a referral to a specialist stop smoking service where high success rates can be achieved utilising combined pharmaceutical and behavioural interventions. However, with recent declines in the availability of this service, there may be a growing role for the dental team to deliver more intensive interventions.

1.4 **Electronic cigarettes**

1.4.1 ***The rise of the e-cigarette***

Although e-cigarettes have become popular recently, the concept goes back over half a century. The first record of an e-cigarette was in 1963 when a US patent was filed for a 'smokeless non-tobacco cigarette' (Herbert A Gilbert, 1963). The patent describes a device not dissimilar to the modern day e-cigarette with the objective of providing a 'safe and harmless means for, and method of, smoking by replacing burning tobacco and paper with heated, moist, flavored air' and that it maintained 'the satisfaction of smoking without any of its disadvantages'. It also proposed that the device could be used therapeutically by 'inhaling warm medication into the lungs in case of a respiratory ailment under direction of a physician'. The invention did not gain popularity, probably due to limitations with the technology at the time. In the 1970s, development slowly continued with Dr Jacobson being one of the first to use the term 'vaping' (smokeless cigs: 'they satisfy', 1980).

The rise in e-cigarette popularity seen during the first years of the twenty-first century is often linked to Hon Lik, a Chinese pharmacist and heavy smoker. He filed a US patent in 2005 for an 'electronic atomization cigarette' that contained 'nicotine without tar', to reduce the 'risk of suffering cancer' (Hon, 2005). Early manufacture of e-cigarettes was limited to China with exports to the US and Europe. As the popularity of e-cigarettes grew, manufacturing developed outside of China. The tobacco industry's interest in the market was relatively slow but eventually became established in 2012 with the purchase of Chinese based company Dragonite International Ltd. by Imperial Tobacco Group PLC for $75 million (Gustafsson, 2013). Commentators liken the tobacco industry's sudden interest to an attempt to avoid the 'Kodak moment', when the world's leading maker of camera film realised the world had gone digital and it was too late to catch up (Kodak moment, 2013).

E-cigarette use in early years (2006-2010) was negligible, although this is hard to quantify as epidemiological surveys did not regularly include questions about e-cigarettes prior to that date e.g. the UK based Smoking Toolkit Study introduced e-cigarette questions in 2011 (West *et al.*, 2018). Over recent years, e-cigarette use has grown considerably with 'ever-use' being estimated at 12.6%, 19.4% and 15% in US (2014), UK (2017) and European (2017) adults respectively (Schoenborn and Gindi, 2015; European Commission, 2017; Office of National Statistics, 2018b). Current (every day or some days) e-cigarette usage rates vary between 2-5.6% in US, UK and European populations (Schoenborn and Gindi, 2015; Coleman *et al.*, 2017; European Commission, 2017; Office of National Statistics, 2018b). UK data report that

men (aged ≥16 years old) are more likely than women to be current e-cigarette users (6.3% compared to 4.9% for women) or ever users (detailed data not provided) of e-cigarettes (Office of National Statistics, 2017). Young adults (16-24 years) were most likely to have tried an e-cigarette and those aged 35-49 years were most likely to be current e-cigarette users (Office of National Statistics, 2017). There are notable gender variations by age groups with more men being current e-cigarette users in the youngest age group (16-24 years, 8.9% versus 2.6%) whilst there were more women e-cigarette users in older age groups (50-59 years, 7.5% versus 5.5%) (Office of National Statistics, 2017).

Prior to e-cigarettes, the most popular quit aid used by smokers was over-the-counter NRT, with e-cigarettes accounting for less than 1% in 2011 (West *et al.*, 2018). During 2011-2013 there was considerable growth, with almost 30% reporting use of e-cigarettes in their most recent quit attempt, by the end of 2013 (West *et al.*, 2018). Since 2013, the rate of growth has plateaued, being 33% in the second quarter of 2018, as demonstrated in Figure 1.5 (West *et al.*, 2018).

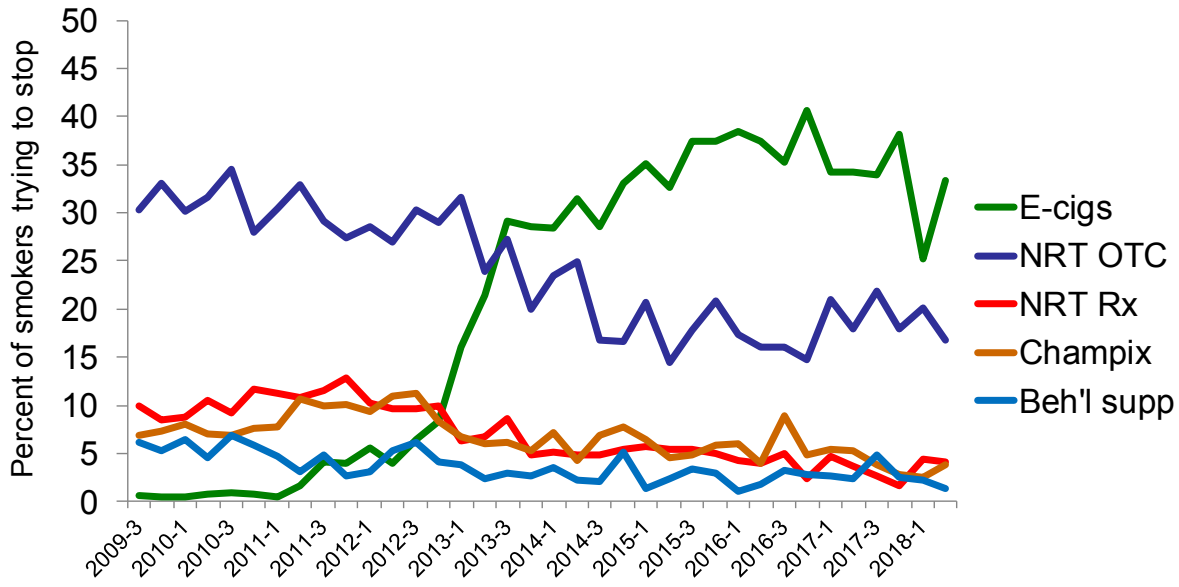

Figure 1.5 Aid used in the most recent quit attempt.

Reproduced from the Smoking Toolkit Study (West *et al.*, 2018). Based on 14050 adults who smoke and tried to stop or who stopped in the past year.

E-cigarette users report a variety of reasons for e-cigarette use with the most common including: as an aid to stopping smoking, because they perceived it be less harmful than tobacco cigarettes or because they could use it at a time or place where tobacco cigarettes were not allowed (Coleman *et al.*, 2017; Office of National Statistics, 2018b).

In adults, e-cigarette users are almost exclusively current and ex-smokers. Very few adult never-smokers report being current e-cigarette users (every day or some days) with prevalence rates of 0.2-0.6% being reported in the US and UK (Schoenborn and Gindi, 2015; Action on Smoking and Health, 2017a; Office of National Statistics, 2018b; West *et al.*, 2018). The smoking status of e-cigarette users is made up of an increasing proportion of ex-smokers and decreasing proportion of current smokers, with approximately 45% using e-cigarettes alongside tobacco (so called dual use) in 2017 (Action on Smoking and Health, 2017a; McNeill *et al.*, 2018; West *et al.*, 2018). It has been noted that the dual usage rates for e-cigarettes are similar to those for NRT alongside burnt tobacco (McNeill *et al.*, 2018; West *et al.*, 2018).

E-cigarette use by young people has been the topic of much concern and debate. Experimentation with e-cigarettes is common in young people with rates of 'ever' e-cigarette use in US high school students being 37.7% (U.S. Surgeon General, 2016), slightly higher than rates seen in the UK which are in the range 7-32% (McNeill *et al.*, 2018). Rates of regular use (defined as weekly use [UK] or 'using e-cigarette on 20 or more days in the last 30 days' [US]) are in the range 1-3% for US teenage populations (U.S. Surgeon General, 2016) and 0.1-0.5% for UK populations (Bauld *et al.*, 2017). Vastly different public health analyses and approaches are taken on this topic. A recent report by the U.S. Surgeon General (U.S. Surgeon General, 2016) concluded that:

- e-cigarette use by youth was a public health concern;
- e-cigarette use by youth was strongly associated with use of combustible tobacco products;
- any form of nicotine was unsafe and could harm the development of the adolescent brain;
- education should be provided (to parents, teachers, coaches and health professionals) on the risks of e-cigarette use among young people.

On the contrary, a recent report from Public Health England (PHE) (McNeill *et al.*, 2018) concluded that:

- despite some experimentation, regular use was rarely seen in never-smokers;

- e-cigarettes did not appear to be undermining the long-term decline in cigarette smoking;
- the 'common liability' hypothesis seems a plausible explanation for the relationship between e-cigarette and smoking initiation;
- harms from long-term nicotine use such as 'snus' and NRT in pregnancy did not lead to health harms;
- widespread misperceptions about the relative risks of nicotine and tobacco need to be addressed and corrected.

A recent UK House of Commons Science and Technology Select Committee reported similar conclusions to the PHE report (House of Commons, 2018). Additionally they called for a medically licensed e-cigarette to be encouraged, by streamlining regulatory processes, in order to make it easier for medical professionals to assist smoking cessation efforts.

This variance in approach has been partly attributed to usage profiles and marketing differences (U.S. Surgeon General, 2016) but is likely to be much wider reaching and complex e.g. cultural differences (Thirlway, 2018).

Although an important topic, the youth debate is not directly relevant to this research project. This project focuses on adults (the age-profile of periodontitis is middle to older aged) who are existing smokers. The issues of youth uptake, use by never-smokers and the gateway effect are not explored in detail within this thesis.

1.4.2 *The technology of the e-cigarette*

E-cigarettes are battery-operated devices that delivers the users with a aerosol(commonly referred to as 'vapour') and are commonly categorised into three generations (McEwan and McRobbie, 2016). First generation e-cigarettes ('cig-a-likes' or 'minis') typically resemble traditional tobacco cigarettes. They are often classed as starter devices, have a low cost and are disposable. Nicotine delivery in these first generation devices is often poor and the battery life is limited. Only 4% of users reported using a disposable e-cigarette in 2017, reducing from 8% in 2014 (Action on Smoking and Health, 2017a).

Second generation e-cigarettes ('tanks') do not resemble cigarettes and often look like pens. They usually contain a tank that is re-fillable by the user. They have larger batteries and are re-chargeable. In 2017, the majority of e-cigarette users (69%) reported using a rechargeable device with a tank or reservoir that is filled with liquids, increasing from 41% in 2014 (Action on Smoking and Health, 2017a).

Third generation e-cigarettes are modifiable ('mods') and have more advanced features such as variable voltage systems and digital readouts, allowing 'vapers' to customise their experience. The technology of this field is constantly changing, often at a rapid pace. A recent example of an innovative design is the 'JUUL' e-cigarette which has a unique presentation (similar to an USB stick) and alternative chemistry, using nicotine salts rather than free-base nicotine (JUUL, 2018). JUUL was the most popular e-cigarette brand in the USA in 2017, and became available for sale in the UK in July 2018 (Bauld, 2018).

The vast majority of e-cigarettes contain e-cigarette liquid (hereafter e-liquid), either in the form of pre-loaded capsules, pre-loaded bottles with which the users top up their device, or do-it-yourself (DIY) kits in which the users mix their own solutions at home. The majority (around 90%) of the solution is made up of a carrier or diluent, usually propylene glycol (PG), vegetable glycerine (VG) or a mixture of the two. It is this diluent that accounts for most of the vapour production. Nicotine is included at varying concentrations, limited to 20mg/ml in the EU but available above 50mg/ml in some other locations. Since both the diluent and nicotine are largely tasteless, flavourings are often added to enhance the user experience. The most popular flavours are fruit, tobacco and menthol/mint (McNeill *et al.*, 2018) but the array of options are extensive with over 7,000 flavours identified in 2014 (Zhu *et al.*, 2014).

1.4.3 *The legal and regulatory framework for e-cigarettes*

The rapid emergence of e-cigarettes onto the market meant that initially there were no specific regulations. In the UK, e-cigarettes were initially regulated as consumer products and were subject to existing product safety regulations (Rough and Barber, 2017). The UK's Medicines and Healthcare products Regulatory Agency (MHRA) subsequently set out plans to regulate e-cigarettes as medicines but the European Union Tobacco Products Directive (TPD) superseded these (European Commission, 2014). The TPD entered into force in May 2014 and was transposed into UK law in May 2016 (UK Government, 2016). The TPD covers product standards and nicotine strength, safety, labelling and packaging, notification and vigilance, advertising and annual reporting. Manufacturers are still able to apply for medical licences for their products but only one has been awarded to date and this product has never been brought to market (Medicines and Healthcare products Regulatory Agency, 2015). During the transposition of the TPD into UK law, additional domestic regulations were added. These included an almost complete marketing ban (print, online, broadcast), age of sale laws and a ban on proxy sales (where an adult would buy an e-cigarette for a young person). All areas of the UK have introduced age restrictions on e-cigarettes that prohibit their sale to, and purchase on behalf of, those aged under 18 years old (Rough and Barber, 2017).

Internationally there are a broad range of approaches to e-cigarette regulation with outright bans on the sale, distribution and importation of e-cigarettes present in some countries e.g. Brazil and Singapore (Rough and Barber, 2017). Others have imposed a *de facto* ban with devices being legal but the sale and possession of nicotine within them being illegal e.g. Australia (Rough and Barber, 2017).

1.4.4 *Efficacy and effectiveness of e-cigarettes for smoking cessation and reduction*

As previously discussed, the most commonly cited reason for e-cigarette use is as an aid to quitting tobacco smoking. There has been a considerable amount of research interest in this field, using several different research designs. Randomised controlled trials (RCTs) randomly allocate smokers to receive different methods of smoking cessation support which include an e-cigarette study arm (Bullen *et al.*, 2013; Caponnetto *et al.*, 2013; Adriaens *et al.*, 2014). Cohort studies include those with a prospective interventional design (i.e. all smokers are provided with an e-cigarette and followed for a period of time), those with a retrospective cohort design (i.e. describes abstinence in smokers who have used an e-cigarette within a specific period), and those which report adverse events only. Systematic reviews with or without meta-analyses have attempted to summarise the research findings and, intriguingly, produced conflicting conclusions. There have been six meta-analyses published to date.

A Cochrane systematic review (Hartmann-Boyce *et al.*, 2016) identified 24 completed studies but included only two RCTs in the meta-analysis (Bullen *et al.*, 2013; Caponnetto *et al.*, 2013). A third study (Adriaens *et al.*, 2014) was included narratively but not in the meta-analysis because of the study design, with all participants receiving an e-cigarette by six months. The authors of the review identified a considerable amount of ongoing research activity with 27 ongoing studies, including 15 potentially eligible RCTs. They concluded that there was evidence that nicotine e-cigarettes helped smokers to quit (RR 2.29, 95% 1.05-4.96), that there were no reported serious side effects (up to 2 years) and that further research was needed. The quality of the evidence was rated as low on the GRADE scale (Guyatt *et al.*, 2008), not because of how the studies were conducted but because of the small number of studies and indirectness (the devices used in these studies were no longer available on the market) (Hartmann-Boyce *et al.*, 2016). Four other meta-analyses (Rahman *et al.*, 2015; Khoudigian *et al.*, 2016; Vanderkam *et al.*, 2016; El Dib *et al.*, 2017) used similar methodology, included the same two studies (Bullen *et al.*, 2013; Caponnetto *et al.*, 2013), and reported comparable findings as detailed in Table 1.2. Conflicting findings were presented in one meta-analysis which concluded that e-cigarettes were associated with significantly less quitting in smokers (Kalkhoran and Glantz, 2016). The difference in these

findings and conclusions seems to be due to methodological issues, particularly regarding the study inclusion criteria. Kalkhoran and Glantz (2016) proposed to conduct a real-world assessment and included 20 studies in their analysis, unlike all the other meta-analyses which included only two RCTs, undoubtedly leading to the different findings. Nineteen of the included studies in the Kalkhoran and Glantz (2016) review were of a non-randomised design, meaning there was no controlling for unexplored confounders. Additionally many of the included longitudinal surveys were at high risk of selection bias. They assessed smoking cessation in e-cigarette users compared with non-users. In the e-cigarettes users group they only included those who were continuing smokers at baseline, meaning those who had already successfully quit using e-cigarettes were excluded from the study population. The resulting sample was potentially biased towards more dependent smokers who may have found it harder to quit. Although many of the systematic reviews included these longitudinal studies, discussing them narratively, only Kalkhoran and Glantz (2016) included them in their meta-analysis and their findings therefore need to be interpreted cautiously. Historically, similar issues have occurred with NRT evaluations when poorly designed observational studies showed negative correlations in contrast to the vast majority of RCTs which demonstrated a strong positive cessation effect, as presented in a Cochrane review including 117 RCTs and over 50,000 participants (Stead *et al.*, 2012). As the number of published RCTs on e-cigarettes increase, it is likely that the meta-analysis results will have improved clarity and strength.

All clinical trials exist on an efficacy (explanatory) – effectiveness (pragmatic) continuum (Thorpe *et al.*, 2009). The majority of the e-cigarettes for smoking cessation clinical trials focus on intervention efficacy (i.e. whether they deliver the expected result under ideal circumstances), although many are moderately pragmatic given the nature of tobacco smoking as a complex behaviour. E-cigarettes present a particular evaluative opportunity, due to their use widely within whole populations, almost as a natural experiment, potentially meaning true effectiveness can be assessed. McNeill *et al.* (2018) suggested that the smoking quitting success rate in England is at its highest level ever observed, with parity across different socioeconomic groups. They concluded that it is plausible that e-cigarettes were contributing to this.

There have been several attempts to estimate the population-level effect of the introduction of e-cigarettes on smoking rates. West *et al.* (2016) completed analysis on English data (2014) and estimated that e-cigarette use within the population had created between 16,000 and 22,000 additional long-term quitters. Beard *et al.* (2016) conducted similar analyses and

found that there was no clear evidence for an association between the prevalence of e-cigarette use by smokers and attempts to quit smoking. However, increased e-cigarette prevalence was positively associated with the success rates of quit attempts (after adjusting for confounding variables) (Beard *et al.*, 2016). They estimated that in 2015 there were an additional 54,288 short- to medium-term (<1 year) and 18,000 long-term quitters (Beard *et al.*, 2016). Analysis of US data has shown similar patterns with Zhu *et al.* (2017) reporting a statistically significant increase in the smoking cessation rate at a population level with increasing e-cigarette use. At a European level, the Eurobarometer survey collected relevant data in 2014 from 28 countries. In a similar fashion to the previously discussed situation with the meta-analysis, conflicting results have been presented from different analyses of the data. Farsalinos *et al.* (2016) reported that 35.1% of current e-cigarette users reported smoking cessation with the help of e-cigarettes. Intensity of e-cigarette use was positively associated with smoking cessation (past experimentation versus current or past use) but there was no comparison to non-users of e-cigarettes. Contrastingly, Kulik *et al.* (2018) reported that e-cigarettes were inhibiting smoking cessation within the European population (OR 0.25, 95% CI 0.18 to 0.35). They (Kulik *et al.*, 2018) discuss as a limitation of their study that the survey data did not include timing of smoking cessation, meaning the sample included people who quit before e-cigarettes were available. They propose that this effect will bias the results towards the null, making the results even more reliable.

In summary, we need further high-quality, well-designed studies to determine the efficacy and effectiveness of e-cigarettes for smoking cessation. At a population level, we need to continue to monitor smoking behaviour in different populations but due to the nature of the evidence produced by such an observational design (it is impossible to conduct a population level RCT) it can only provide evidence of associations and not of causation and will be open to different interpretations.

Study	Studies included in the analysis	Follow up period	Management of loss to follow-up	Cessation effect estimate:	Notes
Hartmann-Boyce *et al.* (2016)	2 RCTs	Results at longest follow-up point	Treated as continuing smokers	RR 2.29 (95% CI 1.05 to 4.96)	Update of previous Cochrane review but with same meta-analysis results (McRobbie *et al.*, 2014).
Rahman *et al.* (2015)	2 RCTs	Results at longest follow-up point	Treated as continuing smokers	RR 2.29 (95% CI 1.05 to 4.96)	
El Dib *et al.* (2017)	2 RCTs	Results at 6 months	Treated as continuing smokers	RR 2.03 (95% CI 0.94 to 4.38)	
Khoudigian *et al.* (2016)	2 RCTs	Results at 6 months and 9 months	Treated as continuing smokers	RR 2.02 (95% CI 0.97 to 4.22)	
Vanderkam *et al.* (2016)	2 RCTs	Results at 6 months	Treated as continuing smokers	RR 1.93 (95% CI 0.92 to 4.01)	
Kalkhoran and Glantz (2016)	15 cohort studies, 3 cross-sectional studies, 2 clinical trials.	Not specified in review methodology. Included studies ranged from 3 months to 6 years.	As managed in the original paper	OR 0.72 (95% CI 0.57 to 0.91)	

Table 1.2 Comparison of meta-analyses of e-cigarettes for smoking cessation.

Adapted from Hartmann-Boyce (2017) conference presentation. RR: relative risk; CI: confidence interval; RCT: randomised controlled trial.

1.4.5 *Safety*

The safety of e-cigarettes covers the device itself, e-liquid constituents, vapour constituents, and encompasses potential harms to the users themselves and to bystanders. With regards to the devices, there have been a number of reports of exploding e-cigarettes resulting in severe injuries, usually burns to the hands and face. McNeill *et al.* (2018) identified 25 published case reports or case series, three from the UK. Overall, the number of incidents is very small and appears to be related to malfunctioning lithium-ion batteries.

The toxic and carcinogenic mixture of tobacco smoke is the biggest cause of cancer worldwide and the most significant source of toxic chemical exposure and chemically mediated disease in humans. The risk of using e-cigarettes, relative to tobacco smoke, is reported to be much lower. For example, several authorities have concluded that e-cigarettes were 'unlikely to exceed 5% of the harms from smoking tobacco' and using the phrase 'vaping is at least 95% less harmful than smoking' is a good way to communicate the large difference in relative risk (McNeill *et al.*, 2015; Royal College of Physicians, 2016; McNeill *et al.*, 2018). Cancer potencies of e-cigarettes were reported to be largely under 0.5% of the risk of tobacco smoking (McNeill *et al.*, 2018).

The potential health risk to users is complex to estimate accurately given the large number of variables: devices, e-liquids, puffing topography and device settings. Cell culture and animal studies are challenging to interpret and to relate to human risk. They provide only weak evidence but can help direct future research. Additionally, the lack of long term clinical data further complicates safety assessments. More robust evidence will eventually come from health outcomes in cohorts of e-cigarette users but these data will take many years to accrue and will also be subject to complex confounding factors i.e. the vast majority of e-cigarette users are previous or current tobacco smokers. A Cochrane systematic review concluded that there were no observed health risks, up to two years, of e-cigarette use within the clinical trials they reviewed (Hartmann-Boyce *et al.*, 2016). Biomarker studies have demonstrated that toxin and carcinogen exposure for e-cigarette users are comparable to those for NRT users, supporting the relative risk estimates previously mentioned (Goniewicz *et al.*, 2017; Shahab *et al.*, 2017). It should be noted that these biomarker studies focus on known carcinogens and toxicants of tobacco smoke and it is plausible that there are unknown carcinogens/toxicants produced by e-cigarettes that have not been assessed in these studies.

Second-hand vapour studies have shown that bystanders can be exposed to low levels of nicotine vapour with levels of other compounds at very low or trace levels (Glasser *et al.*,

2017). McNeill *et al.* (2018) concluded that there have been no identified health risks to bystanders of passive vaping.

E-cigarette flavours have been a particular focus of attention. The flavours used in e-liquids are generally recognised as safe (GRAS) but this is in relation to eating or drinking, rather than inhalation following heating (Royal College of Physicians, 2016). An example of a flavour that has caused concerns is diacetyl, producing a buttery flavouring, and potentially causing bronchiolitis obliterans ('popcorn lung'). This has been the topic of many media stories in the UK and internationally (Macrae, 2015; Sifferlin, 2015). Diacetyl is present in tobacco smoke at levels hundreds of times higher than that observed in e-liquids and since tobacco smoking is not a risk factor for this rare disease, it seems unlikely that diacetyl in e-liquid will pose a significant risk. The MHRA chose to ban diacetyl in e-liquids within the UK (Medicines and Healthcare products Regulatory Agency, 2016b), highlighting how a synthetic product such as e-liquid can be easily modified when potentially undesirable components are identified.

Conflicting views of the evidence exist with heavy criticism of the first PHE report (McNeill *et al.*, 2015) by several prominent individuals (Gornall, 2015; Lancet, 2015; McKee and Capewell, 2015). Glantz and Bareham (2018) criticise the '95% safer' statement in their review paper. They question the credibility of the authors, implying financial conflicts of interest, which were previously refuted (Ann McNeill, 2015). They (Glantz and Bareham, 2018) accept that e-cigarettes deliver lower levels of carcinogens than tobacco cigarettes but highlight that cardiovascular and non-cancer lung disease kill more smokers than cancer, discussing the limited evidence for these risks with e-cigarettes. They conclude that, in their opinion, 'it would not be surprising if e-cigarettes impose half (or more) of the overall long-term risks as those from conventional cigarettes'.

In summary, the relative health harms from e-cigarettes compared to tobacco cigarettes appear relatively small at present. As with any drug delivery device, there will be absolute health risks and research should focus on identifying these, allowing products to be modified to the safest possible forms. Finally, it is notable that oral health harms have scarcely been mentioned in the health harms debate; this is surprising given the established relationship of many oral diseases with tobacco smoking and the mouth being the first contact point for e-cigarette vapour.

1.4.6 *Effect on oral health*

The harmful effects of tobacco smoke on oral health are extensive and well documented (see section 1.2.3). The potential effects of e-cigarette vapour on oral tissues and disease pathology are currently unknown. From our understanding of the constituents, the hypothesis is that e-cigarette vapour is significantly less damaging than tobacco smoke. For example, nicotine at the levels found in e-cigarettes is non-toxic to oral cells *in vitro* (see chapter 2) and has been used clinically in the form of NRT for several decades. Adverse effects (e.g. soreness and ulcers) from orally administered NRT are well documented and it would be expected that e-cigarettes would have a similar risk profile (Mills *et al.*, 2010). Nonetheless, the current evidence base for e-cigarette effects on oral health is limited and consists of laboratory studies of cell cultures, small 'pilot' clinical studies and adverse reactions data.

In vitro studies on oral cells

There are a number of laboratory-based studies on the exposure of oral cells to different conditions i.e. e-cigarette vapours. One of the first of these studies investigated DNA damage in cells exposed to e-cigarette vapour and concluded that e-cigarette vapour was cytotoxic to epithelial cell lines (Yu *et al.*, 2016); press releases from this study reported that e-cigarettes were no better than smoking regular cigarettes (EurekAlert!, 2015). This study was subsequently heavily critiqued in the mass media (Bauld, 2015) and also in a commentary we published (Holliday *et al.*, 2016) because of several methodological and reporting deficiencies. A critical factor omitted from the results, discussions and conclusions (as well as from the majority of the resulting press attention) was that the authors were unable to complete the tests on the cells exposed to cigarette smoke due to its high toxicity. Reference was only made to this briefly within the methods section where the authors describe only being able to expose cells to cigarette smoke for 24 hours, due to the level of toxicity. In contrast, the cells exposed to e-cigarette vapour were cultured for up to 8 weeks, with the cell culture solution (containing the relevant e-cigarette vapour extract) refreshed every three days. Somewhat misleadingly, three of the six figures within the results section display the results of the cigarette smoke alongside the results of the e-cigarette vapour. Figure 1.6 is a bar chart taken from the study presenting DNA double strand breaks as measured by γ-H2Ax immunofluorescence. When reading these graphs the reader would likely draw the conclusion that the e-cigarette vapour caused similar levels of damage to cigarette smoke. In fact what these graphs are showing is a comparison between cells exposed to cigarette smoke for 24 hours against cells exposed to e-cigarette vapour for much longer periods (168 hours in the example given in Figure 1.6). The figure legend partially acknowledges this, stating that

cigarette smoke results ‘are shown for comparison’ but what is meant by this could have been made clearer to the reader. A simple alternative conclusion from the results of this study is that epithelial cells can survive in e-cigarette vapour extract (refreshed every three days) for 8 weeks but only 24 hours when exposed to cigarette smoke. However, the study does show that in *in vitro* conditions e-cigarette vapour is not inert and exposure can lead to cytotoxic and DNA damaging effects, although the clinical relevance is challenging to interpret.

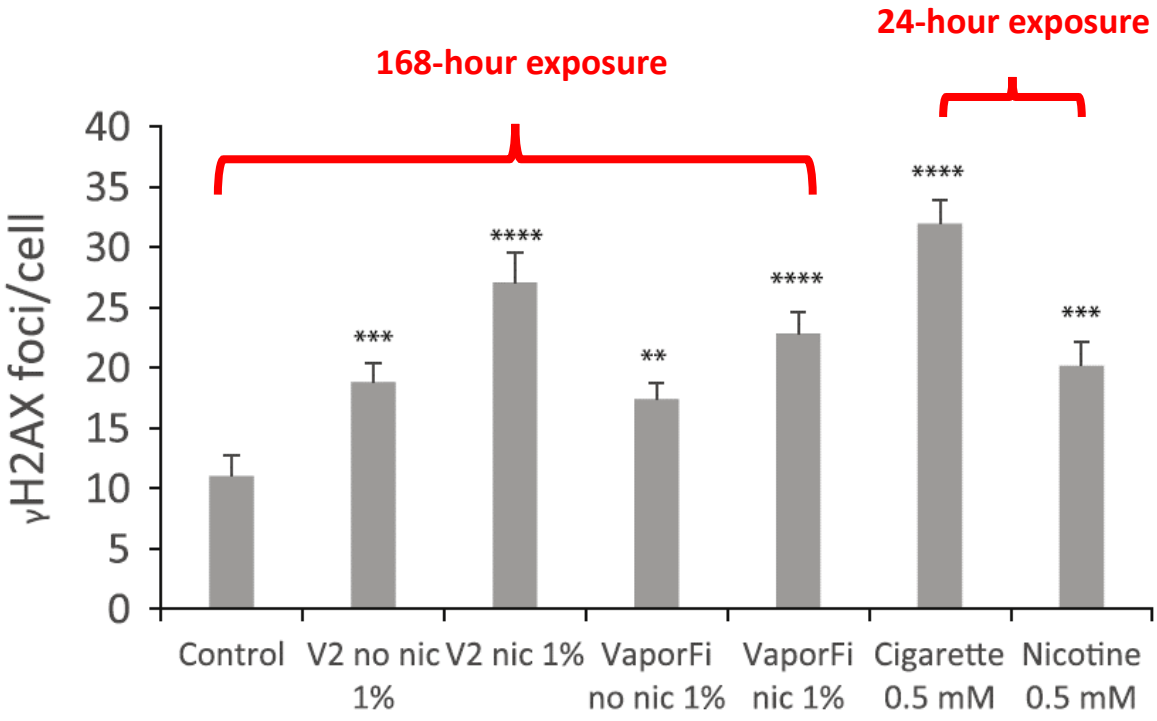

Figure 1.6 DNA double strand breaks in epithelial cells.

Figure adapted from Yu *et al.* (2016) and presents DNA double strand breaks as measured by γ-H2Ax immunofluorescence in an epithelial cell line exposed to different conditions. V2 and VaporFi conditions are different e-cigarette devices either with or without nicotine. Supplementary annotations are added in red to highlight the different exposure times, crucial to the interpretation of the graph, but omitted from the original publication. **P<0.05, ***P<0.001, ****P<0.0001

A number of comparable laboratory studies have investigated a range of parameters, often with similar limitations. A few studies exposed periodontal fibroblast cell cultures directly to e-liquid and reported the e-liquids to be cytotoxic (Sancilio *et al.*, 2016; Sancilio *et al.*, 2017) with menthol flavour being the most harmful (Willershausen *et al.*, 2014). Other studies have tried a more realistic approach by exposing cell cultures to smoke or vapour (Sundar *et al.*, 2016; Yu *et al.*, 2016; Rouabhia *et al.*, 2017). Sundar *et al.* (2016) exposed oral epithelial and periodontal fibroblast cell cultures to e-cigarette vapour and reported increased oxidative and carbonyl stress and inflammatory cytokine release. Unfortunately, they had similar methodological issues to Yu *et al.* (2016) with a lack of detail about the exposure conditions, the absence of a tobacco smoke control and poor choice of exposure conditions. They (Sundar *et al.*, 2016) varied both flavour and nicotine concentration simultaneously meaning that no useful comparisons could be drawn as illustrated in Figure 1.7. Rouabhia *et al.* (2017) reported e-cigarette vapour to cause cell shape modification and increased L-lactate dehydrogenase activity in gingival epithelial cell cultures (no tobacco smoke control).

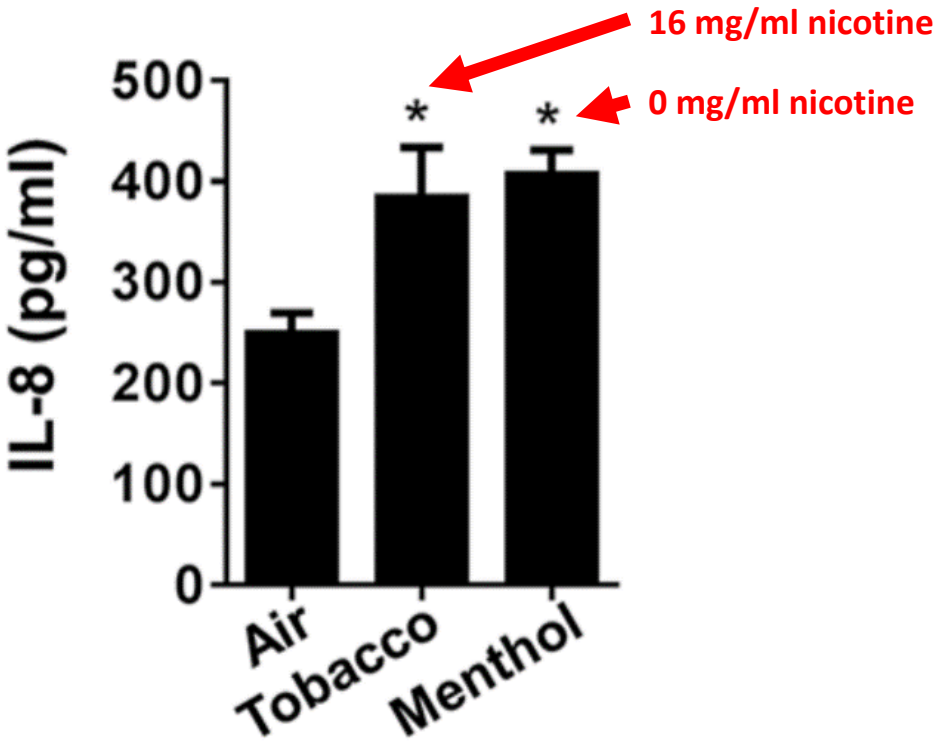

Figure 1.7 Inflammatory response to e-cigarette vapour in periodontal ligament fibroblasts.

Figure adapted from Sundar *et al.* (2016) and presents interleukin-8 (IL-8) production by periodontal ligament fibroblasts exposed to air, tobacco flavour e-cigarette vapour and menthol flavour e-cigarette vapour. Supplementary annotations are added in red to highlight the difference in the nicotine concentrations of the two conditions, important to the interpretation of this graph. * $P < 0.05$

Plaque biofilm studies

As previously discussed, tobacco smoking has significant effects on the oral biofilm leading to an environment primed towards periodontitis. Only one published study to date has investigated the effect of e-cigarette aerosol on the oral biofilm (Stewart *et al.*, 2018). They (Stewart *et al.*, 2018) investigated the buccal oral biofilm in tobacco smokers, e-cigarette users and controls (non-users). They found the oral (buccal) biofilm was comparable in e-cigarette users and the controls, unlike in tobacco smokers who had increased proportions of pathogens. However, this was a small study with only ten participants in each group and the authors called for validation in larger cohorts. No published studies have investigated subgingival plaque biofilm as relevant to periodontitis. In the absence of published studies, there are a number of conference abstracts that have reported on this topic (Ganesan *et al.*, 2016; Ganesan *et al.*, 2017a; Vieth *et al.*, 2017). Ganesan *et al.* (2016) examined the subgingival plaque biofilm in periodontally healthy subjects and concluded that the microbiome of e-cigarette users was virulence rich. They also conducted *in vitro* experiments which reportedly demonstrated that nicotine exposure of health-compatible biofilms lead to upregulation of virulence factors. In a later abstract (seemingly from the same study) they concluded that 'risk-for-harm with e-cigs may be similar to or greater than smoking' (Ganesan *et al.*, 2017b). In another abstract, the same research group reported that those using e-cigarettes as a cessation tool had distinct bacterial community shifts in their subgingival plaque biofilm (Vieth *et al.*, 2017). In-depth analysis of these studies is not possible due to their format as conference abstracts, and they should be interpreted cautiously. However, the findings suggest that e-cigarette vapour may have effects on the subgingival plaque biofilm and this needs to be further investigated in larger-scale clinical studies.

Clinical studies on oral health

There are a growing number of 'pilot' level non-randomised clinical studies investigating oral health outcomes (Franco *et al.*, 2016; Reuther *et al.*, 2016; Tatullo *et al.*, 2016; Wadia *et al.*, 2016; Javed *et al.*, 2017a; Al-Aali *et al.*, 2018). Methodological issues with these pilot studies are discussed in detail later (see section 3.2). Although none of these studies were designed or appropriately powered to demonstrate clinical outcomes, they indicated improvement in oral health when tobacco smokers switched to vaping e-cigarettes (Franco *et al.*, 2016; Tatullo *et al.*, 2016; Wadia *et al.*, 2016; Javed *et al.*, 2017a).

A cross-sectional survey of over sixty-five thousand Korean school students examined three unconventional self-reported outcomes: 'gingival pain and/or bleeding', 'cracked/broken teeth' and 'tongue/inside-cheek pain' (Cho, 2017). They reported no association between e-

cigarette use and ‘gingival pain and/or bleeding’. They reported an association between ever and current e-cigarette use and ‘cracked/broken teeth’ and between current e-cigarette use and ‘tongue/inside-cheek pain’. As acknowledged by the author, there are several limitations in the study design with likely unknown confounders. They also proposed several unusual mechanisms for the effects reported which are outwith conventional understanding. For example, they suggest nicotine has effects on dental pulp cells and increases pulpal inflammation leading to ‘cracked/broken teeth’. Pulpal inflammation would not be considered a common cause of cracked teeth.

Adverse reactions data

No population-based studies exist for adverse reactions. A recent review of the Yellow Card Scheme in the UK found very few reports (McNeill *et al.*, 2018), although this may be a under-representation given the MHRA classification of e-cigarettes (Medicines and Healthcare products Regulatory Agency, 2016a). Research studies record adverse events and the most frequently reported have been mouth and throat irritation, most commonly dissipating over time (Hartmann-Boyce *et al.*, 2016). Survey data report similar findings including a dry mouth (Etter and Bullen, 2011a; Dawkins *et al.*, 2013). Hartmann-Boyce *et al.* (2016) suggest that the common oral adverse effects are likely caused by PG (a humectant) and nicotine (which has a hot/peppery taste).

1.4.7 *Views of the public and profession*

There are a wide range of potential influences on public opinion, including: traditional media, social media, government approaches, regulations and healthcare professionals’ advice. Given the novel nature of e-cigarettes there has been much media attention, often with conflicting and confusing messages. McNeill *et al.* (2018) provide examples of circumstances when front page headlines have been based on suboptimal studies and often misreported. Conflicting messages have also been provided by public health agencies with Figure 1.8 demonstrating contrasting public health campaigns in England and California.

Figure 1.8 Contrasting public health approaches to e-cigarettes as shown through promotion campaigns.

Contrasting public health approaches to e-cigarettes as shown through promotion campaigns. Both left images are from the "Wake Up" campaign by California Department of Public Health in 2015. These adverts tell users to 'wake up' to the risks from e-cigarette use and states that they are producing the next generation of addicts. The upper right image is from the "Stoptober" campaign by Public Health England in 2017. This campaign promoted the e-cigarette as a method of stopping smoking in posters and also a television advert. The lower right image is from a Cancer Research UK awareness pilot campaign in Greater Manchester in 2018 aiming to improve the public's knowledge and harm perception of e-cigarettes.

These factors have undoubtedly contributed to the observed trend of increasing perceived relative harm of e-cigarettes compared to tobacco cigarettes. There has been an increase from 7% (2013) to 26% (2017) of those perceiving e-cigarettes to be more or equally harmful (Action on Smoking and Health, 2017a). The data suggest that concerns about the health harms of nicotine are contributory to this and common across tobacco cigarettes, NRT and e-cigarettes. Although it is well established in the evidence base that none or a very small part of the risk of smoking comes from nicotine, only a small proportion (7.5%-12.9%) of adults correctly select this answer in surveys (Action on Smoking and Health, 2017a; McNeill *et al.*, 2018). Similarly, public perceptions of the cancer risk of nicotine are at odds with the scientific data i.e. nicotine is considered non-carcinogenic (World Health Organisation, 2014) and NRT is on the World Health Organisation list of essential medicines (World Health Organisation, 2017). An international study tracked public perception over 12 years, across four countries (US, UK, Canada and Australia) and reported that only approximately 40-50% of respondents correctly answered that nicotine in cigarettes does not cause cancer, with the UK having slightly lower misperceptions more recently (McNeill *et al.*, 2018).

Healthcare professionals will be exposed to the same influences as the general public but are also likely to have specific professional influences such as journals (peer reviewed and non-peer reviewed) and outputs from professional organisations. We conducted a recent survey of dental professionals with similar findings to those from the general public. Approximately a third (31%) of respondents were of the opinion that e-cigarettes were more or equally harmful than cigarettes and half reported becoming less positive about their use over the previous 12 months (Ahmed *et al.*, 2018). This is in keeping with a recent survey that reported rates of 43% and 36% for dental students in one American and one Spanish dental school, respectively, who held the opinion that e-cigarettes were more or equally harmful than cigarettes (Martín Carreras-Presas *et al.*, 2018). The authors of this paper take a negative stance on e-cigarettes, perhaps reflective of their geographical location (mainly California). For example, they allude to a 'misperception' that e-cigarettes are a potential smoking cessation tool. They criticise the close-to-half of the students who agreed that e-cigarettes could be a smoking cessation aid, calling for further education, particularly of the 'proven toxicity to multiple tissues including pulmonary and oral mucosa'. They cite no evidence on the effectiveness or otherwise of e-cigarettes within their paper. They also incorrectly talk about the 'largely unsupervised marketing and manufacturing of e-cigarettes' but confusingly later discuss in detail the regulations that do exist in the United States (US) and European Union (EU) around marketing and manufacturing.

A number of professional dental organisations have provided opinions or guidance regarding e-cigarettes which present a range of opinions (Table 1.3). It is unclear to what extent these have influenced dental professionals but the lack of consensus clearly demonstrates the need for further research and dissemination.

Organisation	Output	Summary of key messages regarding e-cigarettes
British Society of Periodontology (2016)	The Good Practitioner's Guide to Periodontology	• Relative effect not yet investigated • Likely to be less harmful to periodontal tissues than conventional cigarettes but not as good as stopping both. • Patients should be made aware of the 'knowledge and evidence gap'
British Dental Association (2016)	Position statement	• E-cigarettes may provide a valuable cessation aid or means of harm reducing for some tobacco users. • Caution that evidence of long-term health effects not yet available • Efforts to minimise uptake by non-users of tobacco • Support current regulatory regime (TPD) • Concerned about adolescents who use e-cigarettes progressing to tobacco smoking. Will continue to monitor 'gateway effect' evidence.
European Association of Dental Public Health (2014)	Conference resolution on the control of e-cigarettes	• Uncertainties around manufacture, safety, marketing, advertising, regulation and long term general and oral health outcomes. • Calls to regulate e-cigarettes as tobacco products to support current tobacco restrictions and to maintain and improve oral health.
The Canadian Dental Hygienists Association (2015)	Position statement	Four recommendations: • Ban on e-cigarettes containing nicotine • Ban on sale to minors

Organisation	Output	Summary of key messages regarding e-cigarettes
		• Ban on flavourings • Ban on use in public places and workplaces
Canadian Dental Assistants Association (2017)	Position statement	Seven recommendations: • Develop new framework for regulating e-cigarettes (+/- nicotine) • Conduct longitudinal studies on health effects • Consider e-cigarettes as posing a significant health risk, unless scientific data proves otherwise • Child-resistant packaging • Distinct packaging from nicotine cigarettes • Strict marketing restrictions, especially for youth • Prohibit flavours that appeal to youth • Ban on flavourings • Ban on use in public places and workplaces
Australian Dental Association (2017)	Letter to government committee	• Much more research is needed to confirm whether the use of e-cigarettes assists quit attempts and does not cause health impacts. • E-cigarettes pose oral health (and general health) dangers as they contain harmful chemicals, including carcinogens.

Organisation	Output	Summary of key messages regarding e-cigarettes
		• Nicotine is a highly addictive substance, has a myriad of short and long-term side effects and is a schedule 7 dangerous poison. • E-cigarettes have not been rigorously assessed and quality and safety is unknown. • Supporting e-cigarettes risks re-normalisation of smoking. • Cite Sundar *et al.* (2016) regarding periodontal health (previously discussed in section 1.4.6 and Figure 1.7). • Patients should only use e-cigarettes after all other options attempted, be urged not to use them indefinitely and refrain from using in the presence of children. • Urges the government to take a 'precautionary principle', adopting tobacco regulations for e-cigarettes.

Table 1.3 Professional dental organisations' outputs on e-cigarettes.

1.4.8 *Other novel nicotine products/ heated tobacco devices*

The alternative nicotine product market is rapidly evolving, involving products beyond e-cigarettes. These include nicotine gels and heated tobacco products. Heated tobacco products (also known as heat-not-burn) are devices that heat tobacco to a lower temperature than combustion, aiming to avoid the harmful products produced by burning. Heated tobacco products have been recently launched by several tobacco companies, starting in Japan and slowly increasing distribution worldwide. As of 2018, in the UK these products were mainly available online, with only a handful of shops selling products.

The evidence base for heated tobacco products is in its infancy. McNeill *et al.* (2018) reviewed the evidence, finding the majority (12 out of 19) of studies were funded by the tobacco industry. Given that combustion is avoided, it is likely that these products expose users and bystanders to less harm than regular tobacco smoke, although the extent is unknown. Only one study (funded by a tobacco company) has been published to date on oral health, investigating staining of resin composite (Zhao *et al.*, 2017). Additionally there are two conference abstracts (also both funded by tobacco companies) investigating dental staining potential (Xiaoyi Zhao *et al.*, 2017; Dalrymple *et al.*, 2018). All these studies conclude that heated tobacco products lead to reduced dental staining compared to tobacco smoke. This is a useful outcome for the manufacturers who can use this in marketing material because it is a cosmetic and not a health claim (health claims would require medical authorisation by the MHRA).

1.5 **Summary**

Tobacco smoking remains one of the main public health issues of our age. Smoking is responsible for increased prevalence and severity of oral diseases, especially periodontitis. Dental professionals have an important role to play in providing SCA to their patients who smoke in order to improve their general health, oral health and treatment outcomes. E-cigarettes are increasingly being used by smokers to cut down or quit tobacco smoking. They potentially offer a vital tool in the tobacco endgame towards a smoke-free future. However, due to their recent introduction the evidence base is still under-developed, particularly in the field of oral health. Well-designed investigations need to be conducted to establish the role of the e-cigarette in smoking cessation or harm reduction within the dental setting and to ascertain any undesirable effects on oral health.

1.6 **Aims and objectives of the thesis**

This mixed methods PhD research aimed to explore the behavioural and biological changes when smokers with periodontitis were provided with an e-cigarette. To achieve this aim the research had four objectives:

1. To systematically review the literature with regards to the *in vitro* effects of nicotine on periodontal cells.
2. To conduct a feasibility randomised controlled trial (external pilot trial) of an e-cigarette intervention within the dental setting in order to address uncertainties regarding eligibility, recruitment and retention rates, to explore the feasibility and acceptability of trial procedures, and to collect data to inform power calculations for definitive trials.
3. To explore perceptions about theory-based factors influencing dentist-delivered SCA.
4. To explore the broad perceptions of dental patients towards e-cigarettes and specifically towards being provided an e-cigarette as part of a smoking cessation intervention within the dental setting.

1.7 **Overview of the thesis**

This chapter has described the background, scientific evidence and public health policy for this area of study. It has provided the rationale for the studies subsequently completed and outlined the aims and objectives of the research.

Chapter 2 presents a systematic review of studies that evaluated effects of nicotine on human gingival and periodontal cells *in vitro*, specifically: cell viability, cell attachment, cell proliferation and inflammatory mediator production.

Chapter 3 describes the methods and findings of a pilot randomised controlled trial providing smokers with periodontitis an e-cigarette as part of a smoking cessation intervention. A range of outcome measures were assessed over a 6-month period.

Theory-based semi-structured interviews were conducted on a purposeful sample of study participants. **Chapter 4** describes the interview methods and findings with regards perceptions about smoking and dentist-delivered SCA. **Chapter 5** presents the findings regarding perceptions towards e-cigarettes and the e-cigarette intervention delivered in the study.

Finally, **Chapter 6** collates the findings from the research conducted, setting them within the context of the existing, albeit limited, evidence base, proposing directions for practice and future research (i.e. definitive studies) and acknowledging the strengths and weaknesses of the research methodologies.

Chapter 2 **Effect of nicotine on human gingival and periodontal cells. A systematic review of the literature.**

2.1 **Abstract**

Introduction

Tobacco smoking is a major risk factor for periodontitis and compromises success of treatment. The specific role of nicotine on periodontitis risk is unclear despite a large number of *in vitro* studies. This study aimed to conduct a systematic review of studies that evaluated effects of nicotine on human gingival and periodontal cells *in vitro*.

Methods

Primary research studies on human gingival or periodontal cells, using nicotine exposure as a variable, with appropriate controls, and published in English were identified up to May 2017. Study data were tabulated and analysed narratively.

Results

Of 317 potentially eligible studies, 39 were included. The median quality assessment score was 8/15. Study designs were highly heterogeneous. IC_{50} values for nicotine (the exposure concentration causing 50% cell death or inhibition of cell growth or other utilised toxicity metric) derived from nine studies ranged from 6 μM to 15.6 mM. Studies investigating cell attachment, proliferation and inflammatory mediator production suggested that effects can be seen at a wide range of nicotine concentrations, but results were often contradictory.

Conclusions

According to findings from *in vitro* studies, nicotine, at levels found in tobacco smokers, nicotine replacement therapy users and e-cigarette users, is unlikely to be cytotoxic to human gingival and periodontal cells, though saliva levels in smokeless tobacco users may be high enough to achieve cytotoxicity. There was limited and contradictory evidence for nicotine effects on cell attachment, proliferation and inflammatory mediator production.

2.2 **Introduction**

Smoking is highly prevalent in many populations worldwide. The harmful effects of smoking on general health have been well documented (Clareboets *et al.*, 2010). Smoking also has significant adverse effects on oral health, with an extensive literature documenting the relationship of smoking to periodontal disease (Tomar and Asma, 2000), wound healing and oral cancers (Vineis *et al.*, 2004).

In 2000, it was estimated that over 50% of all cases of periodontitis could be attributed to cigarette smoking (Tomar and Asma, 2000). Smokers are 2-8 times more susceptible to periodontitis than non-smokers (Palmer *et al.*, 2005; Johnson and Guthmiller, 2007) and five times more likely to suffer from tooth loss as a result of periodontitis during long-term periodontal maintenance (Chambrone *et al.*, 2010). Smokers have poorer responses to both non-surgical and surgical periodontal therapies compared to non-smokers (Papantonopoulos, 2004; Johnson and Guthmiller, 2007; Chambrone *et al.*, 2009). Similarly, it has been shown that smokers who quit smoking during periodontal therapy achieve improved clinical outcomes compared with those who continue to smoke (Preshaw *et al.*, 2005; Rosa *et al.*, 2011).

The mechanisms linking smoking and periodontitis have been the focus of numerous *in vitro* studies that have investigated tobacco smoke and its constituents. Whole tobacco smoke has been shown to be highly toxic to oral cells (Zhang *et al.*, 2009) with significant disruption to cellular functions (Semlali *et al.*, 2011).

There have been previous attempts at reviewing the *in vitro* literature in this field (Palmer *et al.*, 2005; Wyganowska-Swiatkowska and Nohawica, 2015). Palmer *et al.* (2005) reviewed the potential biological mechanisms underlying the effects of tobacco smoking on periodontitis. With regards to nicotine specifically, they concluded that ‘nicotine may be unfairly blamed for most of these properties’. In previous decades, this was of little consequence and classifying nicotine as harmful was useful in presenting a simple tobacco control public health message. However, in the modern environment with the availability of NRT and new nicotine delivery technologies (such as e-cigarettes) the effect of nicotine in isolation is of much more relevance.

The *in vitro* studies that have investigated the effect of nicotine in isolation on periodontal cells have often reported contradictory results. Authors have sometimes selectively identified studies, presenting widely differing viewpoints. For example Wu *et al.* (2013) stated

'nicotine, the main toxic component in tobacco, was confirmed as the main effect of smoking on periodontal tissue destruction' whereas Checchi *et al.* (1999) concluded 'nicotine by itself is toxic only at concentrations higher than that found in plasma and crevicular fluid of heavy smokers'. To the best of our knowledge there has not been a systematic review conducted on the *in vitro* effects of nicotine on periodontal cells despite the large number of studies published.

The aim of this systematic review, therefore, was to evaluate the *in vitro* effects of nicotine on human gingival, periodontal and oral epithelial cells, specifically: cell viability, cell attachment, cell proliferation and inflammatory mediator production.

2.3 **Materials and methods**

The PRISMA statement, checklist (Appendix A- Supplementary Figure S1) and flow diagram (Figure 2.1) were utilised in this review. A search protocol was developed *a priori* following discussion between all members of the research team (Richard Holliday, Philip Preshaw and James Campbell). The focussed question for the review was: In *in vitro* conditions, does nicotine exposure, compared to no nicotine exposure, lead to changes in cell viability, attachment, proliferation or inflammatory mediator production in human gingival and periodontal fibroblasts and epithelial cells?

This question was constructed according to the PICOS framework (Table 2.1).

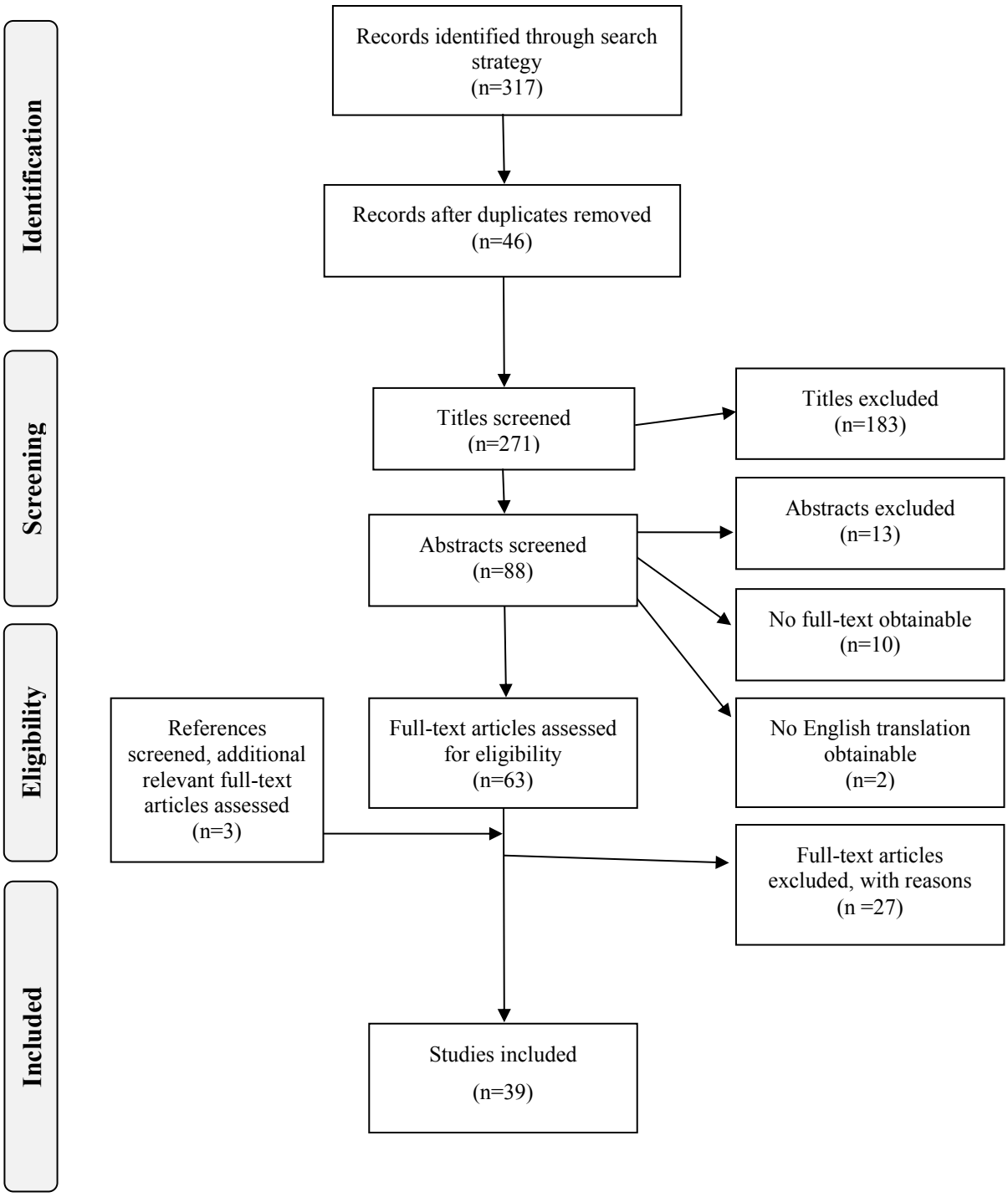

Figure 2.1 Flow chart of included and excluded studies (PRISMA).

PICOS	
Population/patient	Human gingival and periodontal fibroblasts and epithelial cells
Intervention/indicator	Nicotine exposure
Comparator/control	No nicotine exposure
Outcomes	Cell viability Cell attachment/adhesion Cell proliferation Inflammatory mediator production
Study design	In vitro, experimental

Table 2.1 Focused research question presented using the PICOS framework.

2.3.1 *Criteria for considering studies for review*

Inclusion criteria for studies were: (i) primary studies on human gingival fibroblasts (HGFs) or human periodontal ligament cells (HPDLCs) or human gingival/oral epithelial cells (HGECs/HOECs); (ii) nicotine exposure as a variable; (iii) inclusion of an appropriate control (no nicotine); and (iv) published in the English language. Animal studies and abstracts without full papers were excluded.

2.3.2 *Search methods for identification of studies*

Electronic searching

The search terms employed in this study were: ((perio$ [All fields] OR gingiva$ [All fields]) AND (fibroblast$ [All fields] OR epithelia$ [All Fields]) AND nicotine). MEDLINE, EMBASE and Web of Science were searched without language restriction up to, and including 31st May 2017.

Unpublished data and hand-searching

Unpublished data were sought by searching a database listing unpublished studies (www.opengray.eu). Additionally, reference lists of any potential studies were examined (i.e. hand searching) in an attempt to identify any further studies that could be considered for inclusion. Bibliographies of review articles, relevant texts, World and European Periodontology Workshops were also screened. A manual search was performed of the Journal of Clinical Periodontology (1974-2017), Journal of Periodontology (1944-2017) and Journal of Periodontal Research (1966-2017).

2.3.3 *Data collection, extraction and management*

Titles and abstracts from the electronic searches were imported into EndNote X8 (Thomson Reuters, New York City, NY, US). Duplicates were eliminated. Titles were screened independently by two reviewers (RH and JC) and those indicating no relevance to this study were excluded. Abstracts were then screened independently by two reviewers (RH and JC). The full texts of potentially eligible studies were then reviewed against the inclusion/exclusion criteria independently by the two reviewers and disagreement resolved by discussion and consultation with a third author if necessary. Data were extracted independently from the full text articles by two reviewers using a piloted data extraction form. Data collected comprised: year of publication, location of first author, funding source(s), cell types studied, 15-item Consolidated Standards of Reporting Trials (CONSORT) quality assessment, cell viability data (assay used, nicotine exposure conditions and results), cell attachment data (assay used, nicotine exposure conditions and results), cell proliferation data

(assay used, nicotine exposure conditions and results) and inflammatory mediator production data (assay used, nicotine exposure conditions and results).

2.3.4 *Assessment of quality in included studies*

A quality assessment was completed on each included study. A 15-item modified CONSORT checklist was used (Faggion, 2012). Developed by Faggion (2012), this checklist is designed for assessing the quality of *in vitro* pre-clinical research and gives a score out of 15 (with a higher score indicating higher quality).

2.3.5 *Data synthesis*

Data were collated into evidence tables, with study characteristics, details of the exposure conditions, details of the assays conducted and quality assessment included. For data analysis, a narrative approach was utilised.

2.4 **Results**

2.4.1 ***Search results and characteristics of included studies***

The flow chart of manuscripts screened is shown in Figure 2.1. A total of 317 potentially eligible studies were identified by the search strategies. Following de-duplication, title screening was completed on 271 studies with 183 studies being excluded at this stage. Abstract screening was completed on 88 studies with 63 progressing to full-text review. An additional three studies were identified from the references of the screened studies. Finally, 39 studies were included in the full data analysis (Appendix B Supplementary Table S1 provides reasons for exclusion of reviewed full-text studies).

The characteristics of the included studies are presented in Supplementary Table S2 (Appendix C). The included studies were published over a 20 year period from 1995 (Tipton and Dabbous, 1995) to 2015 (Dinos *et al.*, 2015; Esfahrood *et al.*, 2015). Studies were conducted in 13 different countries (based on first author location) with researchers in the USA (Tipton and Dabbous, 1995; Johnson and Organ, 1997; Tanur *et al.*, 2000; Wendell and Stein, 2001; Fang and Svoboda, 2005; Olson *et al.*, 2005; Zhou *et al.*, 2007; Johnson *et al.*, 2010; San Miguel *et al.*, 2010; San Miguel *et al.*, 2012; Gao *et al.*, 2013; Dinos *et al.*, 2015), South Korea (Lee *et al.*, 2005; Lee *et al.*, 2008; Lee *et al.*, 2009; Kang *et al.*, 2011; Kim *et al.*, 2012; Lee *et al.*, 2013; Park *et al.*, 2013) and Japan (Nakao *et al.*, 2009; Takeuchi *et al.*, 2010; Kashiwagi *et al.*, 2012; Nakata *et al.*, 2013; Takeuchi-Igarashi *et al.*, 2014) publishing the greatest numbers of studies per country.

2.4.2 ***Quality assessment***

The median (interquartile range [IQR]) quality assessment score of the 39 assessed papers was 8.0 [1.0], with a theoretical range of scores between zero and 15. The lowest score was six (Alpar *et al.*, 1998; Giannopoulou *et al.*, 1999) and the highest score was nine (Tipton and Dabbous, 1995; Johnson and Organ, 1997; Checchi *et al.*, 1999; Fang and Svoboda, 2005; Mahanonda *et al.*, 2009; Nakao *et al.*, 2009; San Miguel *et al.*, 2010; Takeuchi *et al.*, 2010; Kashiwagi *et al.*, 2012; San Miguel *et al.*, 2012; Silva *et al.*, 2012; Nakata *et al.*, 2013; Park *et al.*, 2013; Wu *et al.*, 2013; Takeuchi-Igarashi *et al.*, 2014; Wu *et al.*, 2014; Esfahrood *et al.*, 2015). Regarding the key methodological domains assessed by the modified CONSORT checklist, all of the studies failed to achieve: sample size determination, random sequence generation, allocation concealment, implementation details, blinding and publication of the full study protocol. Supplementary Table S3 (Appendix D) provides detailed breakdowns of the quality assessment for each study.

Regarding funding sources for published studies, six studies did not provide any details about funding (Alpar *et al.*, 1998; Ciapetti *et al.*, 1999; Olson *et al.*, 2005; Ho and Chang, 2006; Zhou *et al.*, 2007; Dinos *et al.*, 2015), two stated that they had received no funding (Kang *et al.*, 2011; Esfahrood *et al.*, 2015), one detailed an individual providing equipment (Giannopoulou *et al.*, 1999), one was funded by a tobacco manufacturer (Gao *et al.*, 2013), one was funded by a tobacco endowment fund (Fang and Svoboda, 2005), and the remainder received funding from various educational, governmental and charitable sources (Appendix C Supplementary Table S2).

2.4.3 *Cell types investigated*

The most studied cell type were HGFs, being investigated in 21 studies (Tipton and Dabbous, 1995; Alpar *et al.*, 1998; Checchi *et al.*, 1999; Ciapetti *et al.*, 1999; Tanur *et al.*, 2000; Wendell and Stein, 2001; Argentin and Cicchetti, 2004; Fang and Svoboda, 2005; Ho and Chang, 2006; Zhou *et al.*, 2007; Nakao *et al.*, 2009; San Miguel *et al.*, 2010; Takeuchi *et al.*, 2010; Kang *et al.*, 2011; Desjardins and Grenier, 2012; San Miguel *et al.*, 2012; Silva *et al.*, 2012; Park *et al.*, 2013; Takeuchi-Igarashi *et al.*, 2014; Dinos *et al.*, 2015; Esfahrood *et al.*, 2015). Fifteen studies investigated HPDLCs (Alpar *et al.*, 1998; Giannopoulou *et al.*, 1999; James *et al.*, 1999; Chang *et al.*, 2001a; Chang *et al.*, 2002; Olson *et al.*, 2005; Lee *et al.*, 2009; San Miguel *et al.*, 2010; Takeuchi *et al.*, 2010; Kim *et al.*, 2012; San Miguel *et al.*, 2012; Lee *et al.*, 2013; Wu *et al.*, 2013; Takeuchi-Igarashi *et al.*, 2014; Wu *et al.*, 2014). HGECs were investigated by eight studies (Johnson and Organ, 1997; Lee *et al.*, 2005; Lee *et al.*, 2008; Mahanonda *et al.*, 2009; Johnson *et al.*, 2010; Kashiwagi *et al.*, 2012; Gao *et al.*, 2013; Nakata *et al.*, 2013), with one study using HOECs (Desjardins and Grenier, 2012). Supplementary Table S2 (Appendix C) provides details of the origin of the cells.

2.4.4 *Nicotine exposure*

Exposure conditions varied among the studies with respect to nicotine concentrations used and the duration of exposure. The nicotine concentrations used varied from 1 nM (Wendell and Stein, 2001; Esfahrood *et al.*, 2015) to 62 mM (Alpar *et al.*, 1998), with a mean (SD) of 4.16 mM (7.92) (median and mode: 1 mM). The exposure time varied from 30 minutes (San Miguel *et al.*, 2012) to 4 weeks (Tanur *et al.*, 2000) with a mean (SD) of 31.2 hours (54.9) (median and mode: 24 hours). Typically, a single dose was administered as diluted pure nicotine added to culture medium. One study administered nicotine hemisulphate (Fang and Svoboda, 2005). Four studies reported subsequent repeat doses of nicotine, all at 24 hour intervals (Alpar *et al.*, 1998; Checchi *et al.*, 1999; Ciapetti *et al.*, 1999; Dinos *et al.*, 2015) but only one of these ran a single-dose control (Alpar *et al.*, 1998).

2.4.5 *Cell viability*

Thirty-one studies investigated cell viability using a range of assays (Tipton and Dabbous, 1995; Johnson and Organ, 1997; Alpar *et al.*, 1998; Checchi *et al.*, 1999; Ciapetti *et al.*, 1999; Chang *et al.*, 2001b; Wendell and Stein, 2001; Chang *et al.*, 2002; Argentin and Cicchetti, 2004; Lee *et al.*, 2005; Ho and Chang, 2006; Zhou *et al.*, 2007; Lee *et al.*, 2008; Lee *et al.*, 2009; Mahanonda *et al.*, 2009; Nakao *et al.*, 2009; Johnson *et al.*, 2010; San Miguel *et al.*, 2010; Takeuchi *et al.*, 2010; Kang *et al.*, 2011; Desjardins and Grenier, 2012; Kashiwagi *et al.*, 2012; Kim *et al.*, 2012; San Miguel *et al.*, 2012; Silva *et al.*, 2012; Gao *et al.*, 2013; Lee *et al.*, 2013; Nakata *et al.*, 2013; Park *et al.*, 2013; Dinos *et al.*, 2015; Esfahrood *et al.*, 2015). Fourteen studies used the MTT (3-(4,5-dimethylthiazol-2-yl)-2,5-diphenyltetrazolium bromide) assay (Chang *et al.*, 2001a; Chang *et al.*, 2002; Lee *et al.*, 2005; Zhou *et al.*, 2007; Lee *et al.*, 2008; Lee *et al.*, 2009; Mahanonda *et al.*, 2009; Kang *et al.*, 2011; Desjardins and Grenier, 2012; Kim *et al.*, 2012; Lee *et al.*, 2013; Nakata *et al.*, 2013; Park *et al.*, 2013; Esfahrood *et al.*, 2015), five studies used the MTS (3-(4,5-Dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)-2-(4-sulfophenyl)-2H-tetrazolium) assay (Johnson and Organ, 1997; Johnson *et al.*, 2010; San Miguel *et al.*, 2010; San Miguel *et al.*, 2012; Silva *et al.*, 2012), five studies used the trypan blue assay (Alpar *et al.*, 1998; Wendell and Stein, 2001; Argentin and Cicchetti, 2004; Mahanonda *et al.*, 2009; Takeuchi *et al.*, 2010), two studies used the neutral red assay (Checchi *et al.*, 1999; Ciapetti *et al.*, 1999), two studies used microscopic observation (Tipton and Dabbous, 1995; Dinos *et al.*, 2015), one study used the sulforhodamine B assay (Gao *et al.*, 2013), one study used the lactate dehydrogenase leakage assay (Ho and Chang, 2006), one study used fluorescent dye assessment (Alpar *et al.*, 1998), and three studies investigated cell viability in preliminary experiments (but methodological details were not provided) (Tipton and Dabbous, 1995; Nakao *et al.*, 2009; Kashiwagi *et al.*, 2012). Supplementary Table S4 (Appendix E) details the principal results.

There was significant heterogeneity between studies with respect to nicotine exposure conditions. However, 17 studies investigated the effect of a 24-hour exposure of nicotine on HGFs (Tipton and Dabbous, 1995; Alpar *et al.*, 1998; Checchi *et al.*, 1999; Ciapetti *et al.*, 1999; Wendell and Stein, 2001; Argentin and Cicchetti, 2004; Takeuchi *et al.*, 2010; Kang *et al.*, 2011; Desjardins and Grenier, 2012; Silva *et al.*, 2012; Park *et al.*, 2013; Esfahrood *et al.*, 2015) or HPDLCs (Alpar *et al.*, 1998; Chang *et al.*, 2001a; Chang *et al.*, 2002; Lee *et al.*, 2009; Takeuchi *et al.*, 2010; Kim *et al.*, 2012; Lee *et al.*, 2013) (studies explicitly on cells from smokers were excluded in this analysis). Data were derived from these studies and all data points combined in Figure 2.2.

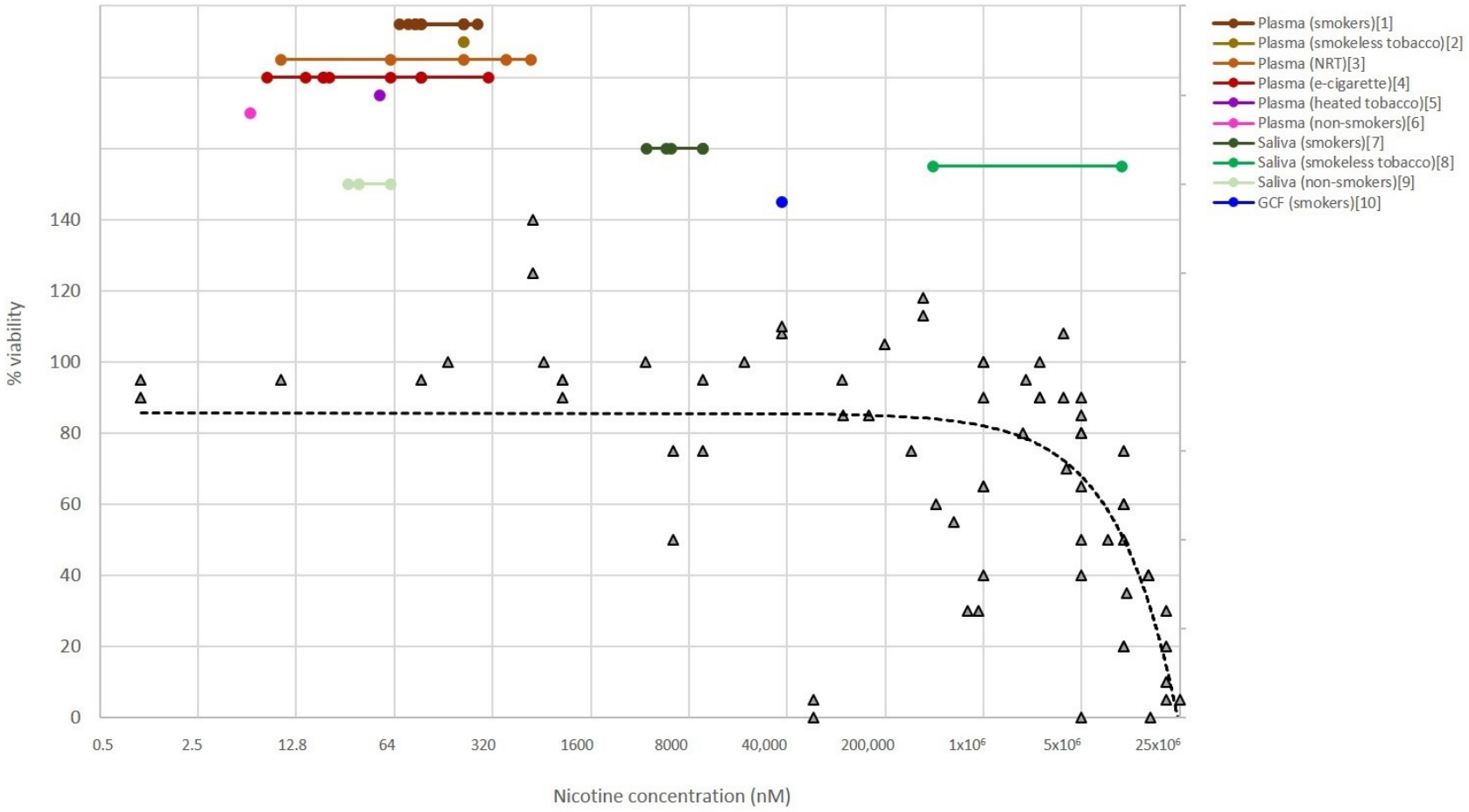

Figure 2.2 Results of cell viability assays carried out on fibroblast cultures.

Results of cell viability assays carried out on fibroblast cultures (not reported to be from smokers) after a 24-hour nicotine exposure; expressed as percentage (of viable cells relative to nicotine-free control) on a logarithmic scale of nicotine concentration. Triangles represent data points derived from the studies; dotted line represents line of best-fit ($Y = -3.5518 \times 10^{-6} X + 85.497$). Normal reported plasma, saliva and gingival crevicular fluid nicotine concentrations are shown for comparison with each marker identifying a study. The corresponding references are: 1=

Bullen *et al*., 2010; Ebert *et al*., 1984; Gourlay *et al*., 1997; Herning *et al*., 1983; Jarvis *et al*., 1984; Russell *et al*., 1981; Vansickel *et al*., 2010; Benowitz *et al*., 1997; Farsalinos *et al*., 2014. 2= Russell *et al*., 1981. 3= Benowitz *et al*., 1997; Bullen *et al*., 2010; Evans *et al*., 2006; Gourlay *et al*., 1997. 4= Bullen *et al*., 2013; Bullen *et al*., 2010; Vansickel *et al*., 2010; Farsalinos *et al*., 2014; Vansickel & Eissenberg, 2013; Dawkins *et al*., 2016. 5= Picavet *et al*., 2016. 6= Jarvis *et al*., 1984. 7= Feyerabend *et al*., 1982; Jarvis *et al*., 1984; Robson *et al*., 2010; Ryder *et al*., 1998. 8= Hoffmann & Adams, 1981. 9= Jarvis *et al*., 1984; Feyerabend *et al*., 1982. 10= Ryder *et al*., 1998.

IC_{50}

IC_{50} (defined as the exposure concentration at which there is 50% cell death or inhibition of cell growth or other utilised toxicity metric) values were identified from 16 studies reporting toxicity data over a range of concentrations for HGFs or HPDLCs (Alpar *et al.*, 1998; Checchi *et al.*, 1999; Ciapetti *et al.*, 1999; Chang *et al.*, 2001a; Wendell and Stein, 2001; Chang *et al.*, 2002; Argentin and Cicchetti, 2004; Lee *et al.*, 2009; Takeuchi *et al.*, 2010; Kang *et al.*, 2011; Desjardins and Grenier, 2012; Kim *et al.*, 2012; Silva *et al.*, 2012; Lee *et al.*, 2013; Park *et al.*, 2013; Esfahrood *et al.*, 2015) (studies explicitly on cells from smokers were excluded in this analysis). One study explicitly reported an ED_{50} value (Alpar *et al.*, 1998), defining this as 'effective $dose_{50}$, concentration of a substance which damages 50% of cells irreversibly'. A further eight studies (Chang *et al.*, 2001a; Chang *et al.*, 2002; Argentin and Cicchetti, 2004; Lee *et al.*, 2009; Takeuchi *et al.*, 2010; Kang *et al.*, 2011; Desjardins and Grenier, 2012; Esfahrood *et al.*, 2015) investigated a sufficient exposure concentration range to allow an IC_{50} value to be derived from the data (Figure 2.3). Seven studies (Checchi *et al.*, 1999; Ciapetti *et al.*, 1999; Wendell and Stein, 2001; Kim *et al.*, 2012; Silva *et al.*, 2012; Lee *et al.*, 2013; Park *et al.*, 2013) did not investigate a sufficient exposure concentration range to allow $IC_{50,}$ determination (Figure 2.3). The IC_{50} ranged from 6 μM to 15.6 mM with a mean (SD) of 7.6 mM (7.0 mM). Two studies reported values in this range for HGECs; Lee *et al.* (2005) reported an IC_{50} value of 300 μM (24 hours) while Gao *et al.* (2013) reported that an EC_{50} ('effective concentration for 50% cytotoxicity') was not reached with 2.8 mM (24 hours).

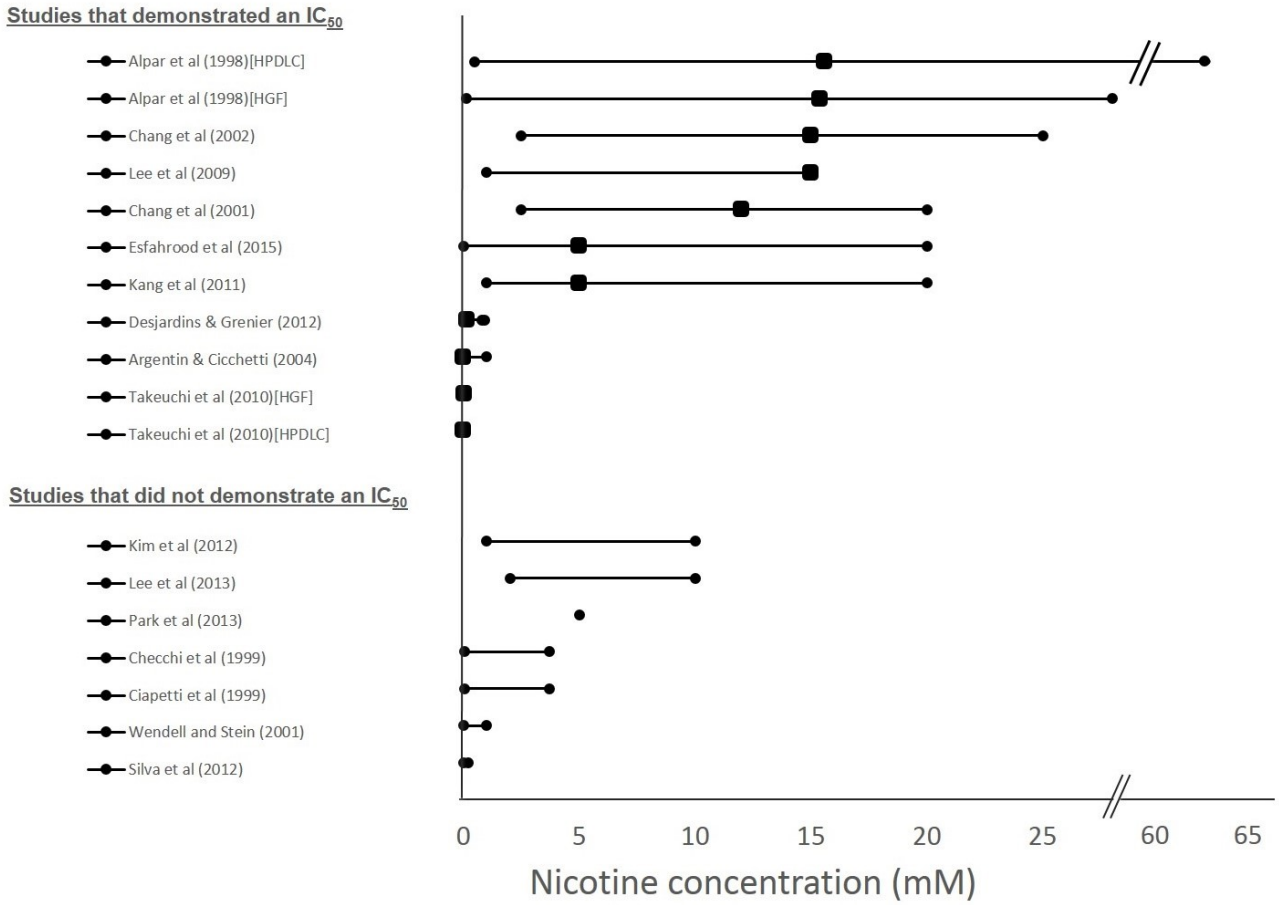

Figure 2.3 IC_{50} of fibroblasts exposed to nicotine.

IC_{50} of fibroblasts (not reported to be from smokers) after a 24 hour nicotine exposure (nicotine concentrations at which a 24-hour exposure causes fibroblast viability to diminish to below 50% relative to nicotine-free control); expressed in milimolar on a linear scale. Squares represents IC_{50} values and the line represents the range of nicotine concentrations used in each study.

2.4.6 *Cell attachment/adhesion*

Four studies investigated cell attachment/adhesion using a range of assays (Giannopoulou *et al.*, 1999; James *et al.*, 1999; Tanur *et al.*, 2000; Esfahrood *et al.*, 2015). Two studied HGFs (Tanur *et al.*, 2000; Esfahrood *et al.*, 2015) and two studied HPDLCs (Giannopoulou *et al.*, 1999; James *et al.*, 1999) (Appendix E Supplementary Table S4). Three different attachment surfaces were used in the studies: plastic (culture plates) (Giannopoulou *et al.*, 1999; James *et al.*, 1999), root surfaces (from extracted teeth) (Tanur *et al.*, 2000; Esfahrood *et al.*, 2015) and glass (Tanur *et al.*, 2000). Two studies used similar nicotine concentrations (620 nM) and reported similar reductions in attachment (approximately 60%) although they had very different exposure durations: 6 hours (Giannopoulou *et al.*, 1999) and 4 weeks (Tanur *et al.*, 2000).

Esfahrood *et al.* (2015) reported reduced attachment at a wide range of nicotine concentrations (1 nM, 1 µM, 1 mM, 5 mM at 24 h) while James *et al.* (1999) reported an approximately 60% reduction in attachment using high nicotine concentrations (31 mM for 24 hours). Both of these studies (James *et al.*, 1999; Esfahrood *et al.*, 2015) used a viability assay to quantify cells remaining attached to a plate under various levels of stress, and it is therefore not readily apparent whether viability, proliferation or attachment is being measured. In summary, although there were conflicting results (widely different results at similar exposure conditions), there was an indication that *in vitro* cell attachment to a variety of surfaces, including tooth roots, can be affected by nicotine concentrations at the nanomolar level.

2.4.7 *Cell proliferation*

Eleven studies investigated the effect of nicotine concentration on cell proliferation. Six studies investigated the effects on proliferation of HGFs (Tipton and Dabbous, 1995; Alpar *et al.*, 1998; Checchi *et al.*, 1999; Ciapetti *et al.*, 1999; Argentin and Cicchetti, 2004; San Miguel *et al.*, 2012), five on HPDLCs (Alpar *et al.*, 1998; Giannopoulou *et al.*, 1999; Chang *et al.*, 2002; Olson *et al.*, 2005; San Miguel *et al.*, 2012), and two on HGECs (Johnson and Organ, 1997; Lee *et al.*, 2005) (Appendix E Supplementary Table S4).

Nine studies reported reductions in cell proliferation (Tipton and Dabbous, 1995; Alpar *et al.*, 1998; Checchi *et al.*, 1999; Ciapetti *et al.*, 1999; Giannopoulou *et al.*, 1999; Chang *et al.*, 2002; Lee *et al.*, 2005; Olson *et al.*, 2005; San Miguel *et al.*, 2012), one of which also observed increased cell proliferation at a lower nicotine concentration (2.3 mM, 24 hours) (Olson *et al.*, 2005). Two studies reported inhibition of proliferation at 3.7 mM over 24 hours (Checchi *et al.*, 1999) and 48 hours (Ciapetti *et al.*, 1999) respectively, but no statistically significant inhibition at lower concentrations of 37 µM and 370 µM. Ciapetti *et al.* (1999)

observed inhibition only after 48 hours exposure, and not at 24 hours. Checchi *et al.* (1999) observed inhibition with 3.7 mM over 24 hours; this did not apply to the cells sourced from smoking subjects over 40 years of age. Two studies reported no statistically significant effect of nicotine exposure on cell proliferation, at respective exposures of 100 nM, 10 μM and 1 mM over 4 and 48 hours (Johnson and Organ, 1997) and 1 μM over 24 to 72 hours (Argentin and Cicchetti, 2004).

Of five studies (Alpar *et al.*, 1998; Giannopoulou *et al.*, 1999; Chang *et al.*, 2002; Olson *et al.*, 2005; San Miguel *et al.*, 2012) which investigated the effect of nicotine on HPDLC proliferation, four studies noted inhibitory effects (Alpar *et al.*, 1998; Giannopoulou *et al.*, 1999; Chang *et al.*, 2002; Olson *et al.*, 2005), with one study (San Miguel *et al.*, 2012) reporting that proliferation was not significantly affected (6, 8 mM; 30 minutes). Chang *et al.* (2002) observed dose-dependent inhibition between 25 μM and 200 μM after 96 hours of exposure to nicotine; all proliferation ceased at concentrations above 400 μM. Alpar *et al.* (1998) also found dose-dependent inhibition at concentrations above 3.9 mM after 24 hours (all proliferation ceased above 31 mM). Only one study reported an increase in cell proliferation (Olson *et al.*, 2005) at 2.3 mM after 24 hours, with inhibition of cell proliferation observed at the higher nicotine concentration of 9.2 mM.

Two studies also investigated cell proliferation indirectly using wound repopulation, or rate of artificial wound closure (Fang and Svoboda, 2005; Dinos *et al.*, 2015). Both studies used gingival fibroblasts on culture plates (Appendix E Supplementary Table S4). Dinos *et al.* (2015) reported significant reduction in wound repopulation after 4 days of exposure to 4 mM nicotine, and at 6 days with as little as 1 mM nicotine. Fang and Svoboda (2005) reported approximately 50% reduction in wound closure rate after 12, 24 and 36 hours of exposure to 0.5 μM nicotine.

2.4.8 *Inflammatory mediator production*

Fourteen studies investigated the effect of nicotine on production of cytokines and other inflammatory mediators relevant in the pathogenesis of periodontitis. Six studies investigated the effects on HGFs (Tipton and Dabbous, 1995; Wendell and Stein, 2001; Zhou *et al.*, 2007; Nakao *et al.*, 2009; Desjardins and Grenier, 2012; Takeuchi-Igarashi *et al.*, 2014), five on HPDLCs (Olson *et al.*, 2005; Kim *et al.*, 2012; Wu *et al.*, 2013; Takeuchi-Igarashi *et al.*, 2014; Wu *et al.*, 2014), four on HGECs (Johnson and Organ, 1997; Mahanonda *et al.*, 2009; Johnson *et al.*, 2010; Kashiwagi *et al.*, 2012), and one on HOECs (Desjardins and Grenier, 2012). The included studies investigated between six (Zhou *et al.*, 2007) and one (Tipton and Dabbous, 1995; Olson *et al.*, 2005; Mahanonda *et al.*, 2009; Nakao *et al.*, 2009; Kashiwagi *et*

al., 2012; Wu *et al.*, 2013) inflammatory mediator(s). The most common mediator investigated was interleukin-8 (IL-8) (Johnson and Organ, 1997; Wendell and Stein, 2001; Mahanonda *et al.*, 2009; Desjardins and Grenier, 2012; Kashiwagi *et al.*, 2012; Wu *et al.*, 2014) followed by interleukin-6 (IL-6) (Wendell and Stein, 2001; Olson *et al.*, 2005; Desjardins and Grenier, 2012), interleukin-1β (IL-1β) (Johnson and Organ, 1997; Wu *et al.*, 2013; Wu *et al.*, 2014), Prostaglandin E_2 (PGE_2) (Johnson and Organ, 1997; Nakao *et al.*, 2009; Kim *et al.*, 2012) and interleukin-1α (IL-1α) (Johnson and Organ, 1997; Johnson *et al.*, 2010) (Appendix F Supplementary Table S5).

With respect to IL-8, two studies (Johnson *et al.*, 2010; Desjardins and Grenier, 2012) showed no effect on IL-8 production in HOECs, HGECs and HGFs cultures with exposure to a relatively wide range of nicotine concentrations (100 nM - 1 mM; 24 hours). Conversely, four studies (Wendell and Stein, 2001; Mahanonda *et al.*, 2009; Kashiwagi *et al.*, 2012; Wu *et al.*, 2014) showed increased IL-8 production in HGFs, HPDLCs and HGECs and 'stimulated HGECs' cultures with exposure to similar nicotine concentrations (1 nM – 1mM; 24 hours).

Almasri *et al.* (2007) investigated the expression of 23 inflammatory mediators on the HGF cell membrane (rather than production/secretion) and reported that nicotine exposure (1.5 mM, 48 hours) resulted in the greatest increased expression of growth-regulating oncogene-α (GRO-α), interleukin-7 (IL-7) and interleukin-15 (IL-15).

Several studies investigated matrix metalloproteinase (MMP) activity following exposure to nicotine. Tipton and Dabbous (1995) reported that collagenase activity in HGFs was statistically significantly increased by nicotine concentrations ≥ 1.5 mM with a 6-day exposure. Both Zhou *et al.* (2007) and Takeuchi-Igarashi *et al.* (2014) reported that nicotine exposures (both nM and mM ranges) had no statistically significant effect on MMP-1 and MMP-2 at time frames up to 48 hours. Kim *et al.* (2012) demonstrated an increase in MMP-2 and MMP-9 (1, 5, 10 mM nicotine for 24 hours) but no statistical tests were performed.

Takeuchi-Igarashi *et al.* (2014) reported significantly increased tissue inhibitors of metalloproteinases- 1 (TIMP-1) levels (in cell culture supernatants) when cells were exposed to nicotine (6.2 nM for 12, 24, and 48 hours) whereas Zhou *et al.* (2007) reported reduced levels of TIMP-1 in nicotine-treated cells (1.5 mM, 48 hours, no statistical tests performed).

2.5 **Discussion**

This systematic review identified a large number of studies that have investigated the *in vitro* effects of nicotine on human gingival, periodontal and oral epithelial cells. We observed high heterogeneity between studies particularly regarding the assays performed, the cells studied and the exposure conditions that were applied. The exposure conditions were particularly varied with nicotine concentrations ranging from 1 nM (Wendell and Stein, 2001; Esfahrood *et al.*, 2015) to 62 mM (Alpar *et al.*, 1998) and exposure time varying from 30 minutes (San Miguel *et al.*, 2012) to 4 weeks (Tanur *et al.*, 2000).

The plasma nicotine concentration of tobacco smokers is well established in the literature with reported concentrations usually being in the range of 70 nM to 200 nM (Russell *et al.*, 1981; Herning *et al.*, 1983; Ebert *et al.*, 1984; Jarvis *et al.*, 1984; Benowitz *et al.*, 1997; Gourlay *et al.*, 1997; Bullen *et al.*, 2010; Vansickel *et al.*, 2010; Farsalinos *et al.*, 2014). Salivary nicotine concentrations of tobacco smokers have been reported from 4 μM to 10 μM (Feyerabend *et al.*, 1982; Jarvis *et al.*, 1984; Ryder *et al.*, 1998; Robson *et al.*, 2010) with much higher levels being reported in smokeless tobacco users (0.43- 9.62 mM) (Hoffmann and Adams, 1981). GCF was found to have a nicotine concentration of 37μM in an analysis of seven smokers (Ryder *et al.*, 1998). Plasma nicotine concentrations in those using NRT have been shown to be similar to or lower than those found in cigarette smokers (Benowitz *et al.*, 1997; Gourlay *et al.*, 1997; Evans *et al.*, 2006; Bullen *et al.*, 2010). With regards to e-cigarettes, several studies reported little effect on plasma nicotine levels (Bullen *et al.*, 2010; Eissenberg, 2010; Vansickel *et al.*, 2010; Bullen *et al.*, 2013) most likely because they used early products and novice users. More recent studies have reported plasma nicotine concentrations that are more similar to those of tobacco smokers: 100 nM (Vansickel and Eissenberg, 2013; Farsalinos *et al.*, 2014) and 300 nM (Dawkins *et al.*, 2016). We are not aware of any published salivary nicotine concentrations in e-cigarette users, although salivary cotinine levels in e-cigarette users have been reported to be similar to those of tobacco smokers (Etter and Bullen, 2011b). A heated tobacco product (heat-not-burn) has been reported to deliver a plasma nicotine concentration of 50 nM (Picavet *et al.*, 2016) (although this paper was published by a tobacco manufacturer). Non-smokers have very low salivary nicotine concentrations (30 nM) (Jarvis *et al.*, 1984).

It is noteworthy that many of the studies used nicotine concentrations in the mM range and these concentrations are only observed *in vivo* saliva of smokeless tobacco users (Hoffmann and Adams, 1981).

The challenge with any *in vitro* research is to interpret the findings in an appropriate way, considering the clinical relevance. For example, when considering cell viability experiments, with nicotine concentrations in the regions observed in smokers, NRT users and e-cigarette users, no effect on cell viability was observed. This suggests that nicotine is not the cytotoxic component of tobacco smoke. Consistent with the findings of an earlier review (Wyganowska-Swiatkowska and Nohawica, 2015), the identified studies in our review only reported a substantial effect on cell viability at nicotine concentrations above approximately 5 mM, and such concentrations would only be seen *in vivo* in the saliva of smokeless tobacco users. From the identified studies, we derived the IC_{50} of nicotine, in HGFs and HPDLCs, and with 24-hour exposure, to range from 6 μM to 15.6 mM (mean [SD]: 7.6 mM [6.8]). The results of our review therefore indicate that the high salivary nicotine concentrations reported in smokeless tobacco users can be cytotoxic to periodontal cells *in vitro*. A previous review also discussed the concerns around smokeless tobacco, periodontal disease and gingival recession (Warnakulasuriya *et al.*, 2010).

It should be remembered that pathological processes are more complicated than simple cell viability assays and in this review we also looked at studies that reported on cell attachment, cell proliferation and inflammatory mediator production. We found that studies reported inhibition of cell attachment with exposure to nM concentrations of nicotine whereas cell proliferation seemed only to be inhibited by higher concentrations of nicotine (in the μM and mM range). Production of inflammatory mediators, including cytokines, appeared to be stimulated by exposure to nicotine at a wide range of concentrations (in the nM to mM range). However, the identified studies often reported contradictory results, which make it hard to draw any definitive conclusions. For example, when considering cell proliferation, for an exposure range between 1-5 mM (24 hours), some studies reported inhibitory effects (Tipton and Dabbous, 1995; Alpar *et al.*, 1998; Checchi *et al.*, 1999), whilst other reported no effects (Johnson and Organ, 1997; Ciapetti *et al.*, 1999) or even increased proliferation (Olson *et al.*, 2005).

It has been postulated by Checchi *et al.* (1999) that some of the differences between studies may be accounted for by varied culture or nicotine exposure conditions. They also proposed that contradictory findings could result from differences in the cell types studied (for example, whether cells were obtained from smokers or non-smokers, or from younger or older individuals, with or without periodontitis, or were commercially-available cell lines, and whether the cells were exposed to nicotine after a variable number of passages). It has also

been suggested than nicotine may have a synergistic action with other substances, for example bacterial toxins (Sayer *et al.*, 1997).

Our quality assessment demonstrated several common deficiencies among the included studies. All lacked any randomisation, allocation concealment and blinding meaning that there was a high risk of potential bias. When considering human studies, the RCT is considered to have the most robust study design for answering research questions. Similar designs can be utilised for *in vitro* studies to reduce the risk of bias (Faggion, 2012). We also noted that many studies failed to mention any limitations of their work. Finally, funding details were absent from a number of the studies, which is particularly important given this field of research potentially involving funding from the tobacco industry. Only one study openly reported being funded directly by the tobacco industry, with another funded by a tobacco endowment fund.

There are some limitations of our systematic review. We limited the scope to nicotine and did not include cotinine. *In vivo*, nicotine is metabolised to cotinine which has a longer half-life than that of nicotine (11-24 hour compared to 30-150 minutes) meaning that *in vivo,* cells could be exposed to cotinine for longer periods with potentially more detrimental effects. Including cotinine was beyond the scope of this review but would be an important consideration for future research. We did not attempt to analyse the effect of study heterogeneity (e.g. by comparing cells from smokers/non-smokers or from patients with periodontitis versus healthy patients), though the scope for doing this was limited given the variable design of the studies that were identified. We limited our review to concentrating on four domains (cell viability, attachment, proliferation and inflammatory mediator production) and there may be other domains that are important, e.g. bacterial susceptibility. We included additional information on wound repopulation and cytokine expression. Although these were not part of our original inclusion criteria, after evaluating the included studies we felt they offered additional important information and included the data in the relevant sections. There is also potential for publication bias e.g. studies which demonstrated no effect of nicotine on the outcome of interest may have been less likely to be published.

2.6 Conclusions

From the studies identified in this review, it appears that nicotine at concentrations found in the plasma, saliva and GCF of tobacco smokers, NRT users and e-cigarette users is unlikely to be cytotoxic to human gingival and periodontal cells in *in vitro* conditions. However, the nicotine concentrations seen in smokeless tobacco users can be cytotoxic in these conditions. Evidence of effects on cell attachment, cell proliferation and inflammatory mediator production suggested that effects could be seen at a wide range of nicotine concentrations but evidence was limited and often contradictory.

2.7 Protocol and registration

There is no registration system for non-clinical systematic reviews. The review protocol can be obtained by emailing the lead author.

2.8 Funding

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2.9 Declaration of interests

The authors declare that there are no conflicts of interest in this study.

Chapter 3 A pilot randomised controlled trial of e-cigarettes for smoking cessation or harm reduction in patients with periodontitis.

3.1 Abstract

Background

Tobacco smoking is a major risk factor for several oral diseases, including periodontitis. Smoking cessation is an important component of periodontal therapy and e-cigarettes are a novel method of smoking cessation that has recently become popular. This pilot trial aimed to assess the viability of delivering and evaluating an e-cigarette intervention for smoking cessation or harm reduction within the dental setting, prior to a definitive study.

Methods

An external pilot 2-armed parallel group, individually randomised controlled trial, with a 1:1 allocation ratio, was conducted over 22 months in the Newcastle Dental Clinical Research Facility. Eligibility criteria included being a tobacco smoker, having periodontitis (≥8 sites with pocket probing depths ≥5 mm) and not currently using an e-cigarette. All participants were provided with non-surgical periodontal therapies and smoking cessation advice. The intervention consisted of an e-cigarette starter kit with brief training. Participants were followed up at 4 weeks, 3 months and 6 months. Proposed outcomes for a future definitive trial, in terms of smoking behaviour and periodontal/oral health were collected. Analysis was descriptive, with 95% confidence intervals presented where appropriate.

Results

Eighty participants were successfully recruited from a range of primary and secondary care dental settings. Participant retention was 73% [95% CI: 62%-81%] at 6 months. The e-cigarette intervention was well received, with usage rates of 90% [95% CI: 77%-96%] at quit date, 78% [95% CI: 63%-88%] at 4 weeks and 53% [95% CI: 38%-67%] at 6 months. 20% [95% CI: 11%-35%] of participants in the control group used an e-cigarette at some point during the study (against instructions). The majority of the outcome measures were successfully collected, apart from a weekly smoking questionnaire which had poor completion rates. Harm reduction (reduction from baseline to 6 months of expired air carbon monoxide) of 6 ppm [95% CI: 1-10] and 12 ppm [95% CI: 8-16] were observed in the control and intervention groups respectively; rates of abstinence (carbon monoxide verified continuous abstinence for 6 months) for the two groups were 5% [95% CI: 1%-17%; control group] and 15% [95% CI: 7%-29%; intervention group].

Conclusions

Data suggest that a definitive trial is feasible and that the intervention may improve smoking quit rates and may have minimal positive effects on periodontal health at 6 months. Insights were gained into how best to conduct the definitive trial.

3.2 **Background**

Periodontal diseases are amongst the most common inflammatory conditions in humans (Tonetti *et al.*, 2017). Periodontitis, an advanced form of periodontal disease, has a multifactorial aetiology but the principal process involves a dental plaque biofilm accumulating in the subgingival environment causing an immune and inflammatory response that leads to destruction of the supporting structures. Consequences of periodontal disease progression include tooth mobility and eventually tooth loss. Severe periodontitis, threatening tooth retention, affects approximately 10% of UK adults; with moderate periodontitis affecting 40-60% (Morris *et al.*, 2011). A recent estimate is that 4.4 million adults in the UK have severe disease (Griffiths and Preshaw, 2014).

There are multiple risk factors for periodontal diseases but tobacco smoking is the most important environmental risk factor. Smoking is thought to affect the periodontal tissues via multiple pathways, including effects on the host immune and inflammatory response, impaired blood flow and microbiological changes. Of particular relevance in the management of periodontitis is the knowledge that smokers who quit are 30% more likely to see clinically significant improvements than individuals who continue to smoke (Chambrone *et al.*, 2013). Dental professionals are advised to provide SCA to all patients who smoke and a range of brief interventions are available as detailed in Table 1.1.

The development of e-cigarettes has added a new option for smokers. Although still limited, there is a growing body of evidence to suggest that e-cigarettes are a useful smoking cessation aid, with effectiveness similar to traditional NRT (Hartmann-Boyce *et al.*, 2016). Likewise, the health risks of e-cigarettes appear to be a fraction of those of tobacco cigarettes with sources stating the risk to be less than 5% (Royal College of Physicians, 2016; McNeill *et al.*, 2018). At a population level, e-cigarettes have been hugely popular with 2.8 million users in the UK as of 2017 (Office of National Statistics, 2018b).

Feasibility studies are an important research design and ensure that future definitive studies are well designed, appropriately powered and deliverable. Feasibility studies can include pilot studies, a miniature test of components of the proposed main study. In some cases this can resemble the proposed main trial very closely as an internal or external pilot trial (see Figure 3.1)

The purpose of pilot studies or trials is to assess feasibility, which is fundamentally different to definitive trials which seek to address efficacy, effectiveness and/or cost-effectiveness.

Pilot studies or trials should focus on descriptive statistics (with confidence intervals) rather than formal hypothesis testing.

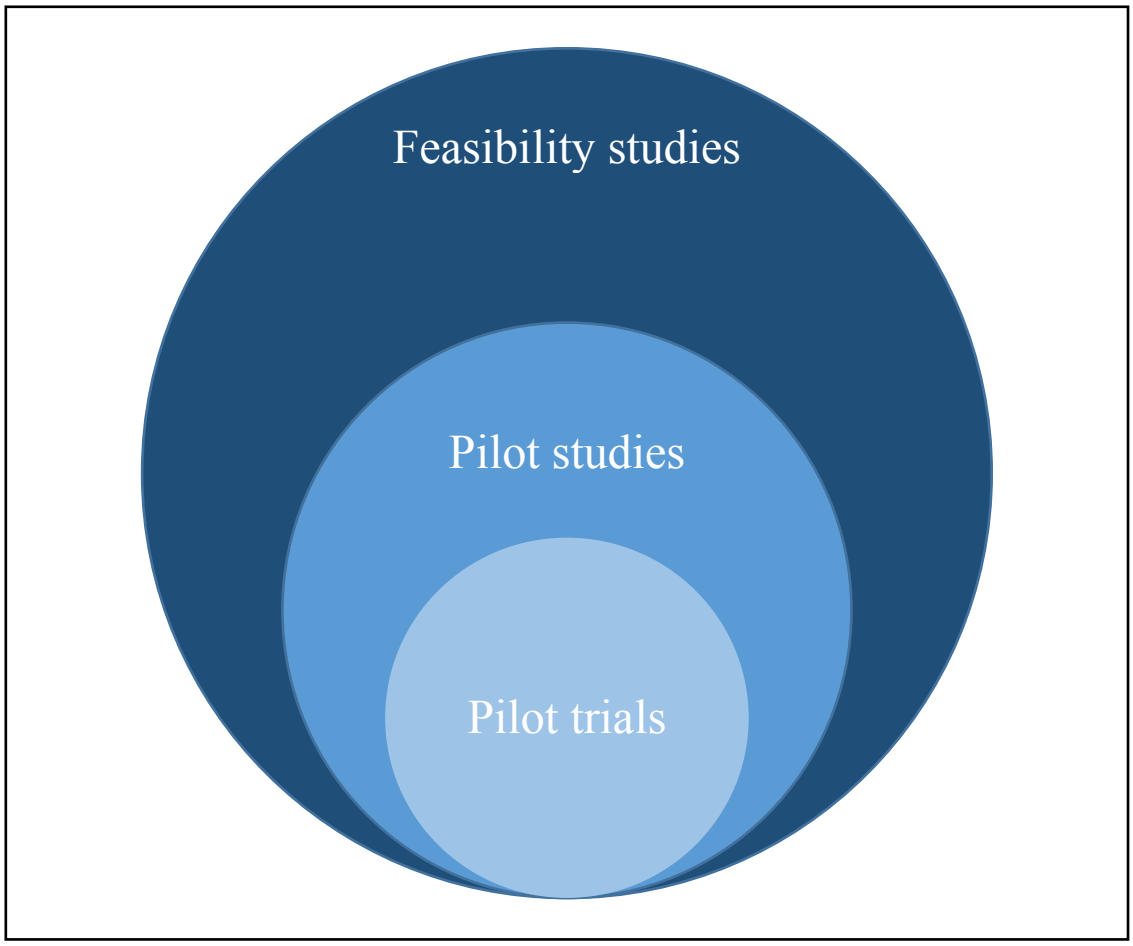

Figure 3.1 Relationship between feasibility studies, pilot studies and pilot trials.

The e-cigarette research field is a good example of how pilot studies can be extremely useful. With e-cigarettes only being available for small number of years, there are many uncertainties regarding the feasibility and acceptability of the intervention and trial processes (e.g. willingness to be randomised). For instance, there were no existing data (at the time of designing the study in 2014/2015) to inform a sample size calculation; pilot studies can be used to estimate the variability of potential primary outcome measures to inform power calculations for future definitive trials.

Within the medical literature, it has been identified that pilot studies, and more particularly pilot trials, are often poorly conducted and inadequately reported. Lancaster *et al.* (2004) summarised these concerns: 'pilot studies play an important role in health research, but they can be misused, mistreated and misrepresented'. Subsequently, the CONSORT group developed an extension to the CONSORT 2010 statement (Moher *et al.*, 2010) to cover pilot and feasibility trials (Eldridge *et al.*, 2016). Although this is primarily directed at RCT designs, the principles are transferrable to other research designs.

Five pilot studies on e-cigarettes and oral health were published from 2016 to 2018 (Reuther *et al.*, 2016; Tatullo *et al.*, 2016; Wadia *et al.*, 2016; Javed *et al.*, 2017a; Al-Aali *et al.*, 2018). Table 3.1 evaluates the reporting quality of these studies against the CONSORT checklist for pilot and feasibility trials, which includes 40 items in 26 sections (Eldridge *et al.*, 2016). Some of the checklist items were not applicable, as the majority of the studies did not randomly allocate participants to groups, so the relevant totals were 28 or 29 items. Overall, these pilot studies performed poorly, only reporting between 5 (out of 28) and 12 (out of 29) checklist items. There were several areas of common weakness. None of the studies had appropriate research questions or objectives. Some of the studies discussed the need for pilot work prior to a definitive study but none clearly outlined how the pilot study would inform the design of that definitive study (other than it being larger). Methods of sample size determination for the pilot study were inadequate in all cases. Estimating the variability of potential primary outcome measures, to inform a definitive study's sample size calculation, is often one of the major reasons for conducting a pilot study. Recommendations suggest that to obtain a robust estimate, outcome data for approximately 30-35 participants per arm are required (Lancaster *et al.*, 2004; Teare *et al.*, 2014). However, none of the pilot studies followed this guidance and instead used a range of invalid methods for determining their sample sizes. For example, Wadia *et al.* (2016) based their sample size calculation on data from a study not using e-cigarettes, proposing it as a method of estimating the effects of e-cigarettes. Javed *et al.* (2017a) also conducted inappropriate sample size determination as

discussed in a letter to the editor (Holliday *et al.*, 2018). All of the studies inappropriately included change in a clinical outcome measures as their primary objective. Most conducted formal hypothesis testing and reported conclusions based upon these, against recommendations by Eldridge and colleagues (Eldridge *et al.*, 2016).

In summary, the pilot studies so far published investigating e-cigarettes and oral health fall far short of the required standard. As Lancaster *et al.* (2004) found in the medical literature, in this field the term 'pilot study' is often being used as an excuse for poor design and inadequate sample sizes. Pilot studies play an important role in health research and tools such as the CONSORT pilot and feasibility trial checklist (Eldridge *et al.*, 2016) should be utilised by researchers and journal editors to ensure the highest levels of research rigour.

Checklist item	Pilot study				
	Al-Aali *et al.* (2018)	**Javed *et al.* (2017a)**	**Wadia *et al.* (2016)**	**Tatullo *et al.* (2016)**	**Reuther *et al.* (2016)**
1a: title identification	X	✓	✓	X	✓
1b: structured summary	X	partly	partly	partly	X
2a: background, rationale for future definitive trial, reasons for pilot study	X	X	partly	X	X
2b: objectives/ research questions	X	X	X	X	X
3a: trial design description	✓	✓	✓	✓	✓
3b: amendments	N/A	N/A	N/A	N/A	N/A
4a: eligibility criteria	✓	✓	✓	✓	partly
4b: settings & locations	partly	partly	✓	✓	partly
4c: participant identification & consent	X	X	✓	X	X
5: intervention details	N/A	N/A	✓	N/A	N/A
6a: outcome details and how linked to 2b	X	X	X	X	X
6b: amendments to outcome measures	N/A	N/A	N/A	N/A	N/A
6c: criteria for judging whether to proceed to future definitive trial (if applicable)	X	X	X	X	X
7a: sample size rationale	X	X	X	X	X

Checklist item	Pilot study				
	Al-Aali *et al.* (2018)	**Javed *et al.* (2017a)**	**Wadia *et al.* (2016)**	**Tatullo *et al.* (2016)**	**Reuther *et al.* (2016)**
7b: interim analysis or stopping guidelines (if applicable)	X	X	X	X	X
8a: sequence generation	N/A	N/A	N/A	N/A	N/A
8b: type of randomisation	N/A	N/A	N/A	N/A	N/A
9: allocation concealment mechanism	N/A	N/A	N/A	N/A	N/A
10: implementation	N/A	N/A	N/A	N/A	N/A
11a: blinding	partly	partly	N/A	N/A	N/A
11b: description of similarity of interventions (if blinding)	N/A	N/A	N/A	N/A	N/A
12: statistical methods	X	X	X	X	X
13a: participant flow	X	X	✓	✓	✓
13b: losses & exclusions after randomisation	X	X	✓	✓	✓
14a: recruitment dates	✓	✓	✓	✓	X
14b: reason trial ended or stopped	N/A	N/A	N/A	N/A	N/A
15: baseline data	N/A	N/A	N/A	✓	N/A
16: numbers analysed	✓	✓	✓	✓	✓
17: outcomes and estimation	X	X	X	X	X
18: ancillary analysis	X	X	X	X	X

Checklist item	**Pilot study**				
	Al-Aali *et al.* (2018)	**Javed *et al.* (2017a)**	**Wadia *et al.* (2016)**	**Tatullo *et al.* (2016)**	**Reuther *et al.* (2016)**
19: harms	✓	✓	✓	✓	X
19a: other important unintended consequences (if relevant)	N/A	N/A	N/A	N/A	N/A
20: limitations	✓	✓	✓	✓	X
21: generalisability	X	partly	partly	X	X
22: interpretation consistent with pilot objectives and findings	X	X	X	X	X
22a: proposed amendments for definitive trial	X	partly	X	X	X
23: registration	X	X	X	X	X
24: protocol	X	X	X	X	X
25: funding	✓	✓	partly	✓	X
26: ethical approval	partly	partly	partly	✓	X
Overall score	**7/29**	**8/29**	**12/29**	**12/29**	**5/28**

Table 3.1 CONSORT 2010 checklist of information to include when reporting a pilot or feasibility trial.

Future rigorous research is required to determine the effectiveness of e-cigarettes as a smoking cessation or harm reduction tool within the dental setting and any subsequent impacts on oral health, specifically with regard to the periodontal tissues and periodontal treatment outcomes. An essential pre-requisite to a definitive trial of the effectiveness and cost-effectiveness of e-cigarettes in this context is a well-designed pilot trial, to address uncertainties regarding eligibility, recruitment and retention rates, to explore the feasibility and acceptability of the intervention and of trial procedures, and to collect data to inform power calculations for the definitive trial.

3.3 Aim and Objectives

3.3.1 *Aim*

The aim of this study was, to assess the viability of delivering and evaluating an e-cigarette intervention for smoking cessation or harm reduction within the dental setting, using a randomised controlled design. The focus of this study was the deliverability, feasibility and acceptability of the e-cigarette intervention and of trial procedures (e.g. randomisation and data collection), rather than the clinical efficacy or effectiveness of the intervention (Eldridge *et al.*, 2016). It did not seek to produce any definitive results relating to the proposed interventions. If the current study indicates that the intervention and trial procedures are feasible and acceptable, a future RCT will be conducted to investigate the clinical effectiveness (in terms of smoking cessation, reduction in cigarettes per day, or periodontal treatment outcome) and cost-effectiveness of e-cigarettes in patients with periodontitis.

3.3.2 *Trial Objectives*

The objectives relate to assessing the feasibility of the future definitive RCT. In particular:

- To estimate trial eligibility rates among our patient population.
- To assess patients' willingness to enter the trial.
- To estimate the recruitment rate; can 80 eligible patients be recruited in a 12-month period?
- To ascertain the retention rate of the participants for 6-month follow-up data.
- To ascertain the randomised group contamination rates (i.e. the extent of cross-over between the two arms of the trial).
- To test a weekly smoking status data collection method.
- To compare, descriptively, novel and traditional periodontal outcome measures. (Novel: Periodontal Inflamed Surface Area [PISA], Periodontal Epithelial Surface Area [PESA]; Traditional: PPDs and Bleeding on Probing [BOP]).
- To compare, descriptively, smoking behaviour and reduction in cigarettes per day.
- To estimate the standard deviation of smoking behaviour and periodontal outcome measures to inform sample size calculation for future definitive trials.
- To test the collection of subgingival plaque for microbiome analysis.
- To test the collection of GCF for inflammatory biomarker analysis.
- To ascertain participant compliance when provided with an e-cigarette.
- To describe tobacco smoking and e-cigarette usage in this patient population.

- To ascertain participant behaviour regarding the use of the e-cigarette: straight nicotine replacement or nicotine cessation device?
- To complete a qualitative process evaluation to establish the views of participants on the provision of e-cigarettes and to finalise the exact characteristics of an e-cigarette intervention for the future definitive study in this patient group.

3.4 **Methods**

3.4.1 ***Design***

This study was a mixed methods feasibility study, comprising a pilot RCT with embedded qualitative process evaluation (presented in chapters 4 and 5). The participants were smokers who had a diagnosis of periodontitis (severe chronic, see section 1.2.1) and who were provided with a smoking cessation intervention alongside their standard periodontal therapy. This feasibility study provided essential information on the practicality of running a full scale trial and provided data on study design, the distributional properties of the proposed outcome measures, e-cigarette acceptability, recruitment and retention. The pilot RCT was an individually randomised, 2-armed parallel group trial with a 1:1 allocation ratio. Outcome assessors (for periodontal outcome measures) were blinded to participant allocation and smoking status. Participants in the control group received usual care (SCA) and those in the intervention group received usual care plus the e-cigarette intervention.

This study adhered to the CONSORT guidance for pilot and feasibility trials (Eldridge *et al.*, 2016) and a completed CONSORT checklist is included (Appendix G).

3.4.2 ***Participants***

This study was conducted within the DCRF of the NDH, a secondary and tertiary care provider.

Study inclusion was limited to those:

- aged over 18 years old;
- smoker of burnt tobacco (≥10 factory-made cigarettes/day or 7 g [0.25 oz]) loose tobacco/day or 14 hand-rolled cigarettes/day);
- not currently using an e-cigarette, or not used one for more than two days in the last 30 days;
- willing and able to come to the DCRF in the NDH for the required study visits;
- having a minimum of 16 natural teeth (excluding third molars);
- being diagnosed with periodontal disease, having interproximal pocket probing depths (PPDs) of ≥ 5 mm at ≥ 8 sites.

Study exclusions were:

- having used an e-cigarette for more than two days in the last 30 days;
- infectious or systemic diseases (myocardial infarction, cerebrovascular accident; phaeochromocytoma; uncontrolled hyperthyroidism; liver or kidney problems; chronic

obstructive pulmonary disease) that may be unduly affected by participation in this study;

- haemodynamically unstable patients hospitalised with severe arrhythmias;
- patients taking the medication adenosine (due to drug interaction);
- lack of capacity to be able to consent to the research project and/or inability to follow study instructions;
- participation in a dental research study within the previous 20 days;
- pregnant by medical history, or nursing;
- received any non-surgical periodontal therapy other than a routine scale and polish in the last 6 months;
- currently undergoing or requiring extensive dental, orthodontic or implant treatment, or treatment for peri-implantitis.

A number of clinical characteristics required further discussions with potential participants before inclusion:

- asthma (severity needed to be assessed, patient made aware that NRT is better than smoking but best to use NRT as a short term stop smoking treatment);
- long term throat disease (severity needs to be assessed, NRT use may exacerbate symptoms);
- stomach ulcer, duodenal ulcer, irritation or inflammation of the stomach or throat (NRT may exacerbate symptoms);
- diabetes mellitus (advised to monitor their blood glucose more closely when initiating treatment, advised to discuss this with their doctor or diabetic nurse specialist);
- those taking theophylline, clozapine and ropinirole medications (metabolised by CYP 1A2 and with a narrow therapeutic window, can be affected by stopping smoking, advised to see their doctor to discuss changing the dose prior to starting the quit attempt).

3.4.3 *Recruitment*

Potential participants were identified through two routes: at new patient and treatment clinics of the NDH or by primary care practitioners. New patient clinics comprised periodontal specific clinics and general restorative dentistry clinics. Treatment clinics comprised mainly the dental emergency clinic but also the student clinics and specialty registrar (StR) clinics. Within the NDH, potential participants were identified by a member of the existing clinical

care team (comprising dentists, hygienists, therapists, dental nurses). The clinical team member contacted the research team (research dentist or research dental nurse) who attended the clinic (if available) to discuss the study with the patient, provide the participant information sheet (PIS, see Appendix H) and arrange appointments. If required, a screening visit was arranged in the DCRF to check for participant eligibility and answer any further questions. Primary care practitioners (general dental practitioners, therapists, hygienists) who identified potentially eligible patients were asked to provide the patient with a PIS and refer them directly to the DCRF (using a dedicated proforma, see Appendix I) for a screening visit.

3.4.4 *Sample size*

No formal sample size calculation was performed for this pilot RCT. Recommendations for good practice in feasibility trials (Lancaster *et al.*, 2004) suggest 30 patients or more are retained in each arm of the trial for provision of data on the proposed primary outcome for the future trial, to provide a robust estimate of the distribution of key study parameters to input to sample size calculations for future definitive trial applications. However, because the attrition rate for randomised patients in this study was not known at the outset (because it was part of the feasibility assessment), 80 patients in total were randomised, 40 to each arm of the trial, to allow for up to 25% attrition while achieving 30 patients per intervention arm with complete study follow-up.

3.4.5 *Intervention: smoking cessation advice*

All participants in this study received SCA delivered by a single treating dentist (myself) alongside the dental care, as part of usual care. This SCA followed the '3 A's': Ask, Advise, Act technique (National Centre for Smoking Cessation and Training, 2012c). A referral to Newcastle stop smoking services was available. This intervention was audio-recorded to allow tests for fidelity. The SCA intervention is fully described in Table 3.3 according to the template for intervention description and replication (TiDieR) checklist (Hoffmann *et al.*, 2014).

3.4.6 *Intervention: e-cigarette intervention*

Participants within the intervention group received the same usual care (SCA) as the control group but also had the offer of an e-cigarette starter kit (as detailed in Table 3.2). The participants were provided with an approximately two-week supply of e-liquid and information on where to buy more themselves. Participants were instructed to use only the Vype brand of e-liquids for the duration of the study, if possible, to match the e-cigarette device provided. At every contact, we monitored what e-cigarette product was being used as

well as the frequency and length of use. The e-cigarette intervention is fully described in Table 3.4 according to the TiDieR checklist (Hoffmann *et al.*, 2014).

Item	Quantity	Details
Vype eTank clearomizer (tank)	2	
650mAh battery	2	
USB charging cable	1	
UK plug	1	
Manufacturer's users' guide	1	
10ml e-liquid	2	Flavour options: Blended Tobacco, Crisp Mint, Dark Cherry and Vpure (flavourless)*. Nicotine strength concentrations: 0mg/ml, 6mg/ml, 12mg/ml, 18mg/ml.

Table 3.2 E-cigarette starter kit contents.

Manufacturer details: The Vype product was produced by Nicoventure Trading Limited (Blackburn, UK) who are a subsidiary of British American Tobacco PLC (BAT, London, UK). The products for this study were procured through our NHS hospital pharmacy either through a NHS wholesaler (AAH Pharmaceuticals, Alliance Healthcare) or directly from the manufacturer (plugs).

*The e-liquid flavours will be referred to as tobacco, mint, cherry and flavourless respectively throughout the rest of this thesis.

3.4.7 *Intervention: periodontal therapy*

All participants, regardless of arm, received identical routine non-surgical periodontal therapy. This followed established and routine clinical management protocols that are already in use in the NDH. Thus, clinical care was not altered in any way by participation in the study. Patients initially underwent a period of patient education and motivation (oral hygiene instruction [OHI]) which followed a structured approach as described by Jönsson et al, 2009. This OHI intervention is fully described in Table 3.5 according to the TiDieR checklist (Hoffmann *et al.*, 2014). The OHI was followed by debridement of the root surfaces of teeth under local anaesthetic. A full mouth debridement (FMD) technique was used in which all the root surface debridement was completed within a short time frame (ideally 24 hours) in line with local (Holliday, 2017) and international (Sanz and Teughels, 2008) guidance.

No.	Item	Definition
1	Brief Name	Smoking Cessation Advice (SCA)
2	Why	A Very Brief Advice intervention, within a medical setting, has been shown to have a significant increase in the rate of quitting (RR 1.66) (Stead *et al.*, 2013a). Oral health care professionals are in an opportunistic position to deliver a smoking cessation intervention. They can provide advice to quit on medical grounds with very powerful patient specific prompts (e.g. radiographs). Specifically for patients with periodontitis, stopping smoking prior to the delivery of their periodontal intervention will lead to significant, visually obvious and relatively rapid improvements.
3	What (materials)	If the patient had a panoramic radiograph this was used as a prompt to demonstrate any periodontal disease diagnosis, bone loss and likely impact of smoking on the mouth. If no radiographs were available then other prompts such as tooth staining and bad breath were used as personal prompts.
4	What (procedure)	The SCA is a short behavioural based intervention based around three domains: • ASK: Ask and record the smoking status (current smokers, ex-smoker, non-smoker)? • ADVISE: Advise on the likely impact of smoking on the mouth, specifically periodontitis (using patient specific prompts where appropriate e.g. panoramic radiograph). Advise on the best way to quitting (the best way of stopping smoking is with a combination of medication and specialist support). • ACT: Act on patient's response. Build confidence, give information and refer. Patients are up to four times more likely to quit successfully with support. A referral was available to the local stop smoking services. A suggested quit date of visit 2 (initial visit of periodontal therapy) was suggested.

No.	Item	Definition
5	Who provided	A dentist provided the SCA. All those providing SCA had completed the NCSCT e-learning module 'Very Brief Advice on Smoking' (National Centre for Smoking Cessation and Training, 2012c).
6	How	The SCA was delivered at an individual level, by the dentist, integrated as part of a dental visit.
7	Where	Dental Surgery, Dental Clinical Research Facility, Newcastle Dental Hospital.
8	When and how much	The SCA was specifically delivered during study visit 1 (the dental visit prior to the commencement of the periodontal therapy). During this visit the periodontal diagnosis was discussed with the patient, oral hygiene instruction given and the SCA provided. The duration of the SCA was meant to be between 2-5 minutes depending on the response of the participant. The SCA was reinforced at each subsequent dental visit, dependent on the individual participant.
9	Tailoring	The duration of the SCA was dependent on the engagement of the individual participant. Participants received supportive advice, at follow up visits, tailored to their level of engagement. As a minimum a 30 second SCA was delivered at each dental visit. As indicated above, prompts were tailored to patient circumstances.
10	Modifications	NA
11	How well (Planned)	The SCA training was delivered by a national organisation. Dentists also received training on discussing the effects of smoking on oral health as part of their undergraduate degrees. The SCA delivered during the first study visit was audio-recorded and a sample checked for implementation fidelity against the SCA flow diagram.

No.	Item	Definition
12	How well (Actual)	A sample of 10 random audio-recordings were checked by a research dental nurse. The average duration was 3 minutes and 12 seconds (ranging from 1 minutes and 10 seconds to 4 minutes and 53 seconds). All the sample contained the three elements of the SCA intervention (Ask, Advise, Act).

Table 3.3 TiDieR checklist: smoking cessation advice.

No.	Item	Definition
1	Brief Name	E-cigarette intervention
2	Why	E-cigarettes have seen a significant rise in popularity in recent years and there is a growing body of evidence that they are an attractive and effective smoking cessation/ harm reduction tool. E-cigarettes are easy for dentists to recommend and/or provide.
3	What (materials)	The participants were provided with a second generation (tank) e-cigarette. A starter kit was provided as detailed in Table 3.2. Participants had a choice of four flavour and nicotine concentrations. An information sheet was provided which provided information on setting up the e-cigarette, and where to purchase further e-liquids and tanks (see Appendix J).
4	What (procedure)	The dentist provided the e-cigarette starter kit and e-liquid to each participant in the intervention arm of the study. They practically demonstrated the e-cigarette set up with each participant. They talked through the information sheets and answered any questions.
5	Who provided	A dentist provided the e-cigarette and training.
6	How	The e-cigarette training was delivered as a conversation with the e-cigarette as a prompt.
7	Where	Dental Surgery, Dental Clinical Research Facility (DCRF), Newcastle Dental Hospital (NDH).
8	When and how much	The e-cigarette intervention was delivered directly following the SCA intervention and was expected to be 10-15 minutes in duration.
9	Tailoring	The e-cigarette intervention was the same for all participants, with patient choice in respect of flavour and concentration of e-liquid respected. Participants were able to request further support at subsequent appointments as required.

No.	Item	Definition
10	Modifications	NA
11	How well (Planned)	The dentist providing the e-cigarette intervention followed the information sheet as a prompt and had a discussion guide (see Appendix K). The e-cigarette intervention was audio-recorded and a sample checked for implementation fidelity.
12	How well (Actual)	A sample of 10 random audio-recordings were checked against the 22 items in the discussion guide (Appendix K) by a research dental nurse. The average duration was 9 minutes and 29 seconds. Nineteen items were present 100% of the time. Item 3 ('You are still free to use any of the other ways to stop smoking on top of this') was absent on one occasion, although this was likely to have been delivered at another non-recorded time point. Items 15 (introducing the users guide) was absent on three occasions, although this was implied by the subsequent use of the users guide. Item 16 (highlighting the manufacturer's users' guide at the back of the box) was absent on three occasions.

Table 3.4 TiDieR checklist: e-cigarette intervention.

No.	Item	Definition
1	Brief Name	Oral Hygiene Instruction (OHI)
2	Why	Obtaining a satisfactory level of oral hygiene is an important factor in the success of periodontal interventions.
3	What (materials)	As appropriate: • Inter-dental cleaning aids: dental floss, inter-dental brushes • Single tufted brush • Manual toothbrush (demo only) • Powered toothbrush (demo only) • Dental demonstration model
4	What (procedure)	The dentist/hygienist presented information on caries and/or gingivitis/periodontitis; oral hygiene instruction was given based on plaque scores. The individual's oral status was reviewed at subsequent visits.
5	Who provided	A dentist or hygienist.
6	How	The OHI was delivered as a face-to-face conversation at an individual level.
7	Where	Dental Surgery, Dental Clinical Research Facility, Newcastle Dental Hospital.
8	When and how much	The OHI was delivered during one of the initial visits. The OHI duration was 5-10 minutes. At subsequent visits further OHI was provided as appropriate, often integrated as part of the periodontal therapy.

No.	Item	Definition
9	Tailoring	The OHI followed the same structure for all participants and was tailored according to the participant's existing level of oral hygiene, level of oral hygiene knowledge and level of engagement.
10	Modifications	NA
11	How well (Planned)	The dentist/hygienist who provided the OHI were experienced practitioners.
12	How well (Actual)	NA

Table 3.5 TiDieR checkist: oral hygiene instruction.

3.4.8 *Overview of study visits*

Participants were asked to attend for six study visits over six months (Figure 3.2 Study design overview). There were no additional visits for research purposes with all visits being in line with normal periodontal therapy and follow-up.

Pre-study visit - screening

As previously detailed (see section 3.4.3), potential participants were identified opportunistically by existing clinical care teams within either the NDH or primary dental services. Potential participants were screened against the study eligibility criteria. Information was provided about the research study and potential participants had the opportunity to ask questions. A research ethics committee (REC) approved participant information sheet was discussed with the participants and a copy provided to take away. Participants had at least 24 hours to consider their willingness to enter the study before signing the informed consent form, with further time available if required.

Baseline (visit 1)- consent, demographics, baseline measurements/samples, randomisation and smoking interventions

If potential participants agreed to participate in the research study, informed consent was taken by an appropriately trained (non-blinded) member of the research team. An informed consent form (see Appendix L) was signed and the participant was provided with a copy for their own records. Demographic information were collected and recorded in a case report form (CRF) by a non-blinded researcher. These data comprised: date of birth, age, gender, ethnicity, occupation, entitlement to free prescriptions, body mass index (BMI), previous smoking habits, previous quit attempts and previous use of stop smoking support or medications (including e-cigarettes). Baseline smoking-related outcome data were collected, comprising: self-reported smoking status, expired air carbon monoxide (eCO), Fagerstrom Test for Nicotine Dependence (FTND) (Heatherton *et al.*, 1991) and the Mood and Physical Symptoms Scale (MPSS) (West and Hajek, 2004). Saliva was collected for salivary cotinine (SC) and salivary anabasine (SA) determination. Baseline oral health related outcome data were collected by a single blinded research dental hygienist and comprised: PPD, modified gingival index (MGI), plaque index (PI), BOP, Clinical Oral Dryness Score (CODS) and the UK Oral Health-related Quality of Life Measure (OHQoL-UK) (McGrath and Bedi, 2002). GCF and subgingival plaque were collected for inflammatory biomarker and microbiological analysis (details of this methodology is detailed in section 3.4.14). Table 3.6 provides a detailed breakdown of the schedule of events throughout the study.

Participants were randomised to either the control or intervention group (see section 3.4.9 for details of the randomisation process). All participants were provided with SCA with those in the intervention group also receiving the e-cigarette intervention.

Quit date (visit 2)- periodontal intervention (part 1)

The non-surgical periodontal intervention was provided using a FMD technique where appropriate. This was delivered over two visits, usually using a split mouth technique (right then left). OHI was provided. This visit was the suggested smoking quit date.

Second treatment visit (visit 3)- periodontal intervention (part 2)

The second part of the FMD periodontal intervention.

4 weeks (visit 4)- SPT, smoking-related outcome measurements and samples

SPT provided as required. Smoking-related outcome data were collected, comprising: self-reported smoking status, eCO, FTND and MPSS. Saliva was collected for SC and SA determination.

3 months (visit 5)- SPT, smoking and oral health related outcome measurements and samples

SPT provided as required. Smoking-related outcome data were collected, comprising: self-reported smoking status, eCO, FTND and MPSS. Saliva was collected for SC and SA determination. Oral health related outcome data were collected by a blinded research dental hygienist, comprising: PPD, MGI, PI, BOP, CODS. GCF and subgingival plaque samples were collected for inflammatory biomarker and microbiological analysis.

6 months (visit 6)- SPT, smoking and oral health related outcome measurements and samples

SPT provided as required. Smoking-related outcome data were collected, comprising: self-reported smoking status, eCO, FTND and MPSS. Saliva was collected for SC and SA determination. Oral health related outcome data were collected by a blinded research dental hygienist and comprised: PPD, GI, PI, BOP, CODS and OHQoL-UK. GCF and subgingival plaque samples were collected for inflammatory biomarker and microbiological analysis.

Event	Visit 1 (baseline)	Visit 2 (quit date)	Visit 3	Visit 4 (4 weeks)	Visit 5 (3 months)	Visit 6 (6 months)
Periodontal outcome measures						
No. teeth	X				X	X
PPD	X				X	X
MGI	X				X	X
PI	X				X	X
CAL	X				X	X
BOP	X				X	X
Microbiological	X				X	X
Inflammatory biomakers	X				X	X
OHQoL-UK	X					X
CODS	X				X	X
Smoking outcome measures						
FTND	X	X		X		X
MPSS	X	X		X		X
eCO	X	X		X		X
SC	X	X		X		X
SA	X	X		X		X
Self-reported smoking status	X	X		X	X	X

Table 3.6 Schedule of events.

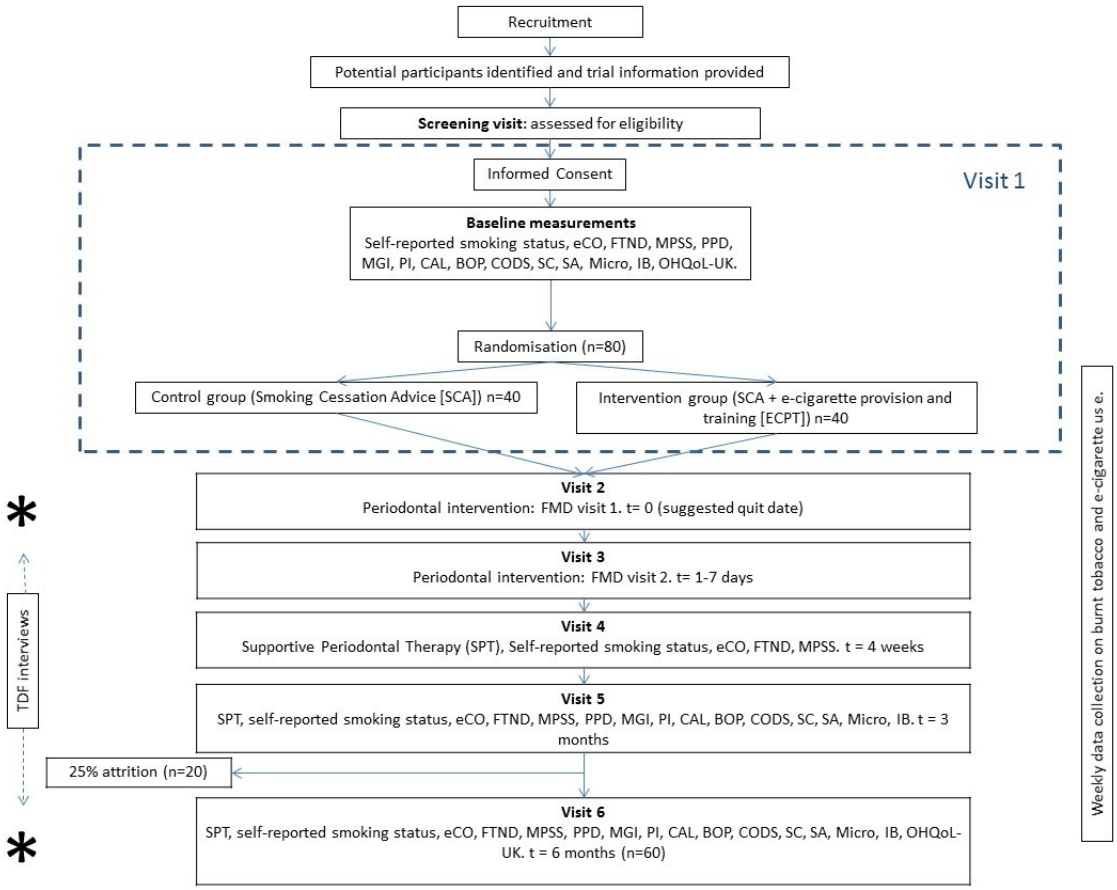

Figure 3.2 Study design overview.

Please note that the participant numbers presented in this figure are estimated numbers and not the actual participant numbers observed in the RCT. The actual participant numbers are presented in Figure 3.5 CONSORT flow diagram.

Abbreviations: eCO- Expired air Carbon Monoxide, FTND- Fagerstom Test for Nicotine Dependence, MPSS- Mood and Physical Symptoms Scale, PPD- Pocket Probing Depths, MGI- Modified Gingival Index, PI- Plaque Index, CAL- Clinical Attachment Loss, BOP- Bleeding on Probing, CODS- Clinical Oral Dryness Score, SC- Salivary Cotinine, SA- Salivary Anabasine, Micro- Microbiological outcome measure, IB- Inflammatory biomarkers, OHQoL-UK- Oral Health Quality of Life Assessment, TDF- Theoretical Domains Framework.

3.4.9 *Assignment of interventions*

Following the assessment of eligibility and completion of informed consent, participants were randomised to the control or intervention group, in a 1:1 ratio using random permuted blocks of variable length. The randomisation allocation schedule was generated by a statistician with no other involvement in the study, to achieve concealment of allocation. Randomisation was performed using a secure password-protected web-based system administered by Newcastle CTU. Randomisation generated a unique 4-digit "Study ID number" for each participant. There were no stratification factors.

3.4.10 *Concomitant care*

Participants in the control group were asked not to use an e-cigarette for the duration of the study, especially during the first 4 weeks. They were asked to sign a commitment form demonstrating that they agreed to this (see Appendix M). It was impractical to completely prohibit e-cigarette use, since they are freely available on general sale. The use of all stop smoking services and cessation aids (including e-cigarettes) was recorded in detail at each study visit for all participants.

Participants in the intervention group were advised to use only the recommended brand of e-liquids for the duration of the study. At each study visit, we monitored which e-cigarette product was being used as well as the frequency and length of use. The participants were free to use other NRT products, either purchased over the counter or provided through the specialist stop smoking services.

3.4.11 *Blinding*

Due to the nature of this study, the participants and care providers could not be blinded to assigned intervention. At each study visit, participants saw the dentist, for any study interventions, and if applicable, the research hygienist, for clinical study measurements.

The outcome assessor, measuring the range of oral health indices, was blind to participants' smoking status and intervention allocation. These study measurements were collected by a trained, blinded, calibrated research hygienist, not otherwise involved in the study. Participants were asked not to disclose their smoking status or methods of smoking cessation to the blinded assessor and were reminded of this prior to every visit by the unblinded research nurse.

3.4.12 *Outcomes and data collection methods*

A range of outcome measures were used to assess both smoking behaviour and oral health; these were selected in anticipation of their inclusion as primary or secondary outcomes in a

future definitive trial. For smoking behaviour, they comprised: self-reported tobacco and e-cigarette use, eCO, SC, SA, FTND and MPSS. For oral health, they comprised: PPD, MGI, PI, CAL, BOP, CODS, PESA, PISA and OHQoL-UK. The data collection method for each outcome is described below.

Self-reported tobacco and e-cigarettes use

Participants were asked to verbally report (to the research dentist [Richard Holliday]) their tobacco and e-cigarette use at visits 1, 2, 4, 5 and 6. For tobacco, details on the quantity (number of cigarettes or weight of loose tobacco per day) and type of tobacco (factory-made, hand-rolled) were recorded. For e-cigarettes, the number of days on which e-cigarettes were used, as well as product details, were recorded.

Cumulative tobacco and e-cigarette use

Participants were asked to complete a weekly questionnaire which asked them to report their average cigarettes/day over the last 7 days. The questionnaire was made available in several mediums to accommodate the participant's preference: short message service (SMS) text message with an embedded link to a mobile web page, email with embedded link, telephone call or a paper version.

Expired air carbon monoxide

A calibrated carbon monoxide monitor (piCO SMOKERLYZER, Bedfont Scientific Ltd, Maidstone, UK) was used to measure eCO at visits 1, 2, 4, 5 and 6. A single reading was taken by a non-blinded member of the research team. A reading of 10 parts per million (ppm) or above signified that the participant had smoked tobacco in the preceding 24 hours (West *et al.*, 2005b).

Salivary cotinine and salivary anabasine

Cotinine is a metabolite of nicotine and SC is a biomarker of nicotine exposure which gives high readings in those using tobacco, e-cigarettes or other nicotine replacement products. A SC reading below 15ng/ml signified a non-user of tobacco or nicotine products (West *et al.*, 2005b). SA is an alkaloid with a very similar chemical structure to nicotine; SA is found in tobacco but not NRT or e-cigarettes. Anabasine was used to confirm if a participant using NRT/e-cigarettes had also obtained nicotine from tobacco. A SA reading below 0.1ng/ml signified that they had not used tobacco (M Doig [ABS Laboratories], personal communication, 3 August 2018) (Jacob *et al.*, 2002; Brown *et al.*, 2014a). This allowed the bio-chemical verification of the self-reported smoking statuses of those who abstained from all nicotine, those using only NRT/e-cigarettes and those still smoking. Saliva samples were

collected at visits 1, 2, 4, 5 and 6 (see section 3.4.14 for complete details of saliva collection methods).

Fagerstrom test for nicotine dependence

This six-item questionnaire is designed to assess the degree of dependence among smokers coming to a smoking cessation clinic (Heatherton *et al.*, 1991). It produces a score between 0-10 with higher scores representing more dependence (see Appendix N). The FTND was completed at visits 1, 2, 4, 5 and 6.

Mood and physical symptoms scale

This 12-item questionnaire assesses cigarette withdrawal symptoms (West and Hajek, 2004). The ratings can be analysed individually or totalled together to give composite scores. Scores were combined to give four scores: MPSS(Mood [M]) [items 1-7], MPSS(Cravings [C]) [items 8 and 9], MPSS(Physical [P]) [items 10-12] and MPSS(total) [items 1-12] (National Centre for Smoking Cessation and Training, 2012b) (see Appendix O).

Smoking abstinence measures

Smoking abstinence was reported in six different categories. In increasing strictness these comprised: self-reported quitter, eCO-verified self-reported quitter, SC/SA-verified self-reported quitter, eCO- and SC/SA-verified self-reported quitter, Russell Standard 6-month quitter based upon eCO (RS6-eCO) and the Russell Standard 6-month quitter based upon eCO and salivary analysis (RS6-S). The RS6 includes six criteria as detailed in Table 3.7.

Russell Standard criteria	Compliance of this study
Six-month follow-up from quit date	Complied fully
Self-reported smoking abstinence over whole follow-up period allowing up to five cigarettes in total	Complied by recording self-reported smoking status at each visit. A two week grace period from the quit date was applied as recommended.
Biochemical validation of abstinence	Complied by using eCO and/or SC/SA validation.
Intention-to-treat analysis with participants counted as smokers if smoking status can't be determined [unless died or moved to an untraceable address]	Complied by using intention-to-treat analysis.
Following up 'protocol violators' and using true smoking status in analysis.	Complied by following up all participants in their original groups.
Blind follow-up	Oral health data were collected by a blinded assessor. Due to the limitations of a doctoral research project it was not possible to collect smoking outcome data blinded. Follow-up rates were reported for each group as recommended.

Table 3.7 Russell Standard outcome criteria in smoking cessation.

Pocket probing depths

A single trained and calibrated hygienist, blinded to group allocation, collected the PPDs using a manual University of North Carolina (UNC)-15 periodontal probe to record the probing depths to the nearest millimetre. Probing depth was defined as the distance from the probe tip (assumed to be at the base of the pocket) to the free gingival margin. This was recorded at six sites per tooth at visits 1, 5 and 6.

Modified gingival index

A gingival index based on the Lobene Modified Gingival Index (Lobene *et al.*, 1986) was used to rate the gingival inflammation on a scale of zero to four. This index was assessed by the blinded research hygienist. Table 3.8 detail the parameters of the scale. This index was recorded at six sites per tooth at visit 1, 5 and 6.

Plaque index

The plaque index of Silness and Loe (1964) was employed to measure plaque (without disclosing), rating it on a scale of zero to three. This index was assessed by the blinded research hygienist. This was recorded at six sites per tooth at visit 1, 5 and 6. Table 3.9 details the parameters of the scale.

Clinical attachment loss

Gingival recession was defined as the distance from the free gingival margin to the cemento-enamel junction. It was recorded to the nearest mm using a manual UNC-15 periodontal probe. Gingival recession was indicated as a positive number and gingival overgrowth was recorded as zero. CAL was calculated by adding the gingival recession and PPD measurements. This measurement was collected by the blinded research hygienist, at visit 1, 5 and 6.

Bleeding on probing

Following probing, each site was assessed for bleeding on probing. If bleeding occurred within 30 seconds of probing, a score of one was assigned for the site, otherwise, a score of zero was assigned. This measurement was collected by the blinded research hygienist, recorded at six sites per tooth at visit 1, 5 and 6.

Clinical oral dryness score

Oral dryness (xerostomia) was measured using a ten-item scale as described by Osailan *et al.* (2012), giving scores from zero to ten. This index was collected by the blinded research hygienist, at visit 1, 5 and 6. Table 3.10 details the ten items on the scale (each item is assigned a score of one if present).

Oral health quality of life assessment

The OHQoL-UK questionnaire (McGrath and Bedi, 2002) was used to measure oral health-related quality of life at visit 1 and 6. The 16 items allow responses in either a positive or negative (bidirectional) manner to a series of statements about the effect of oral health on specific aspects of respondents' daily lives (see Appendix P). The responses range from "very bad" (score 1) to "very good" (score 5). Responses are then summed to give a total score, or can also be summed within three sub-domains (physical [items 1-4, 15-16], social [items 6-8, 12-13] and psychological [items 5, 9-11, 14]) as described in the literature (McGrath and Bedi, 2002; Durham *et al.*, 2013). The lower the score the poorer the OHQoL. McGrath and Bedi (2001) reported this questionnaire to have good validity and reliability for assessing the impact of oral health on life quality.

Score	Description
0	Absence of inflammation
1	Mild inflammation; slight change in colour, little change in texture of any portion of but not the entire margin or papillary gingival unit
2	Mild inflammation; but involving entire margin or papillary unit
3	Moderate inflammation; glazing, redness, oedema and/or hypertrophy of margin or papillary unit
4	Severe inflammation; marked redness, oedema and/or hypertrophy of marginal or papillary gingival unit, spontaneous bleeding, congestion, or ulceration

Table 3.8 Modified gingival index (Lobene *et al.*, 1986).

Score	Description
0	No plaque
1	A thin film of plaque at the gingival margin which may be seen only after running the probe along the tooth surface
2	Moderate accumulation of plaque deposits which can be seen with the naked eye
3	Extensive accumulation of plaque deposits

Table 3.9 Plaque index (Silness and Loe, 1964).

Item	Description
1	Mirror sticks to buccal mucosa
2	Mirror sticks to tongue
3	Frothy saliva
4	No saliva pooling in floor of mouth
5	Tongue shows loss of papillae
6	Altered/smooth gingival architecture
7	Glassy appearance of other oral mucosa, especially palate
8	Tongue lobulated/fissured
9	Active or recently restored (last 6 months) cervical caries (>2 teeth)
10	Debris on palate (excluding under dentures)

Table 3.10 Clinical oral dryness score (Osailan *et al.*, 2012).

3.4.13 *Examiner alignment and assessment*

A single examiner recorded all of the oral health measurements throughout the study. The examiner was an experienced research dental hygienist, blinded to treatment arm. In order to reduce examiner bias and increase the validity of the study results, an intra-examiner clinical reproducibility assessment exercise was conducted on two oral health measurements: PPD and gingival recession. Repeat measurements were taken in pre-specified quadrants on six participants and the percentage agreement of duplicated measurements were calculated (Hefti and Preshaw, 2012). Results demonstrated good agreement with over 98% of measurements within 2 mm for both parameters (Table 3.11). Bland-Altman plots were generated (Figure 3.3 and Figure 3.4) and there was no indication of proportional bias (Bland and Altman, 1986).

Oral health measurement	**Exact agreement (%)**	**Agreement +/- 1mm (%)**	**Agreement +/- 2mm (%)**
PPD	66.7	92.8	98.1
Gingival recession	82.4	92.0	98.1

Table 3.11 Intra-examiner clinical reproducibility assessment.

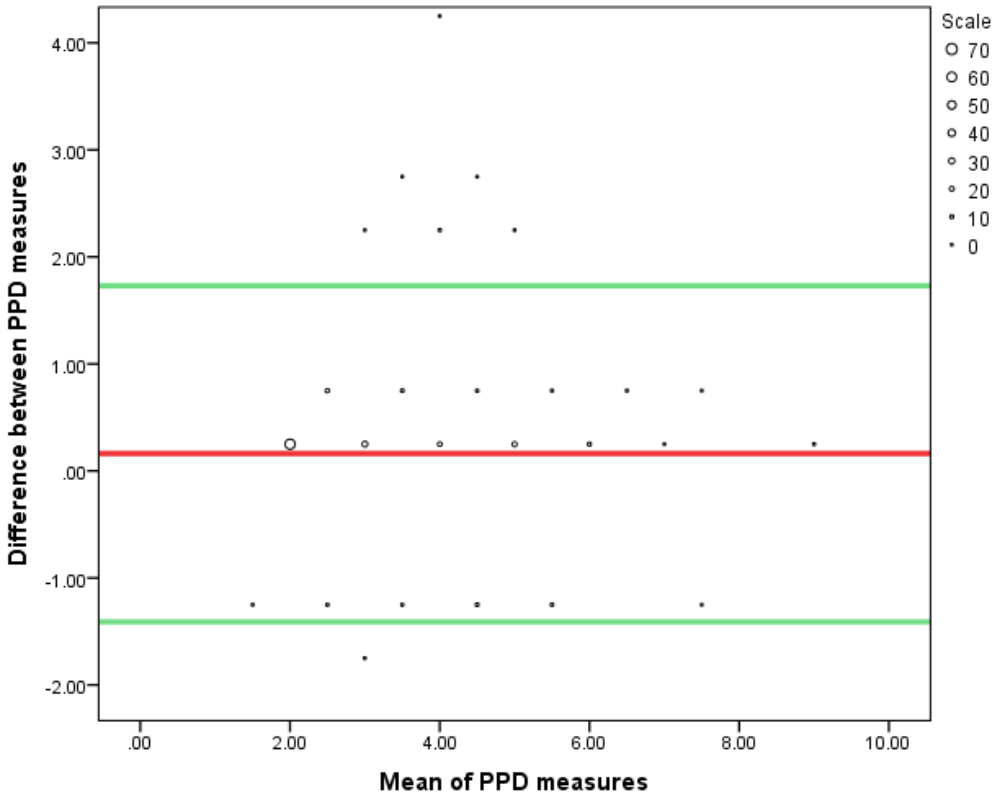

Figure 3.3 Bland-Altman plots for PPD.

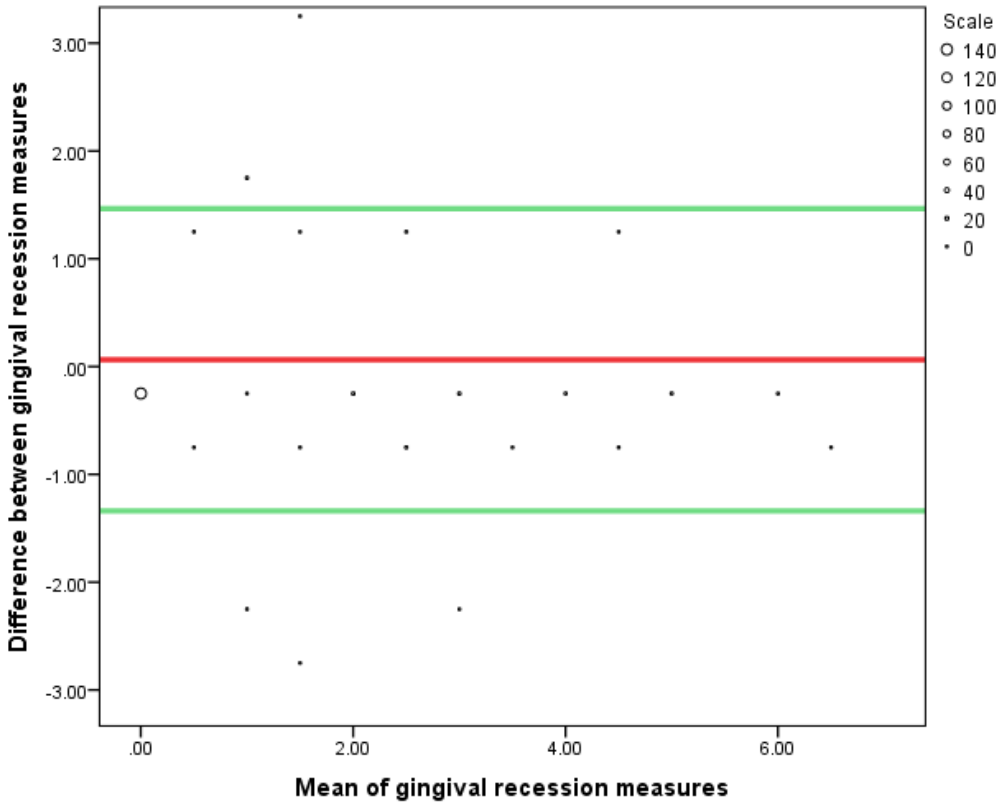

Figure 3.4 Bland-Altman plots for gingival recession measurement.

3.4.14 *Collection and analysis of biological samples*

Saliva was collected at each study visit (excluding visit 3) to allow determination of SC and SA. GCF and subgingival plaque were collected alongside the periodontal indices at visits 1, 5 and 6. GCF was used for biomarker analysis whilst the subgingival plaque was used for the microbiological analysis.

Saliva collection

Saliva samples were obtained at least one hour following the last consumption of food, drink or medication by the participant and at least one hour following the last episode of oral hygiene (toothbrushing, flossing, mouthrinses etc). Samples were collected at any time during the working day. Participants were seated in the dental chair, without distraction, noise, or conversation. A Salivette® (Sarstedt, Nümbrecht, Germany) was labelled with a sample identifier number and date. Participants were advised to remove the stopper, whilst holding the suspended insert and to place the swab under the tongue by tipping the Salivette® close to the mouth. Participants were not allowed to touch the swab. The swab was left in place until 'soggy' before transferring directly from the mouth to the suspended insert. The stopper was replaced and the Salivette® immediately placed on ice, transferred to the laboratory and placed in a -80ºC freezer.

Saliva analysis

The saliva was analysed for concentrations of cotinine and anabasine. This analysis was conducted at an external commercial laboratory (ABS Laboratories,Welwyn Garden City, UK). Samples were stored in -80ºC freezer within the Cell and Molecular Biosciences Laboratory (Newcastle University) until transfer. Samples were transferred to ABS Laboratories in one shipment at the end of the study using a courier service. The samples were classified as 'Category B' samples and transported accordingly (Health and Safety Executive, 2009).

GCF collection

Two periodontal pockets (5≤ PPD≤8 mm) were identified and recorded in the CRF. The sites were isolated using cotton rolls and any supragingival plaque was removed with curettes and cotton pellets. Prior to collecting the GCF, two pre-labelled cryovials were prepared chairside. A Periopaper strip (Oraflow Inc., New York, USA) was placed carefully into the sulcus of the identified site until mild resistance was felt. The strip was left in place, holding the cheek retracted for 30 seconds. The strips was immediately transferred to separate sterile, dry labelled microcentrifuge tubes. Any excessively blood-soaked strips were discarded and new

samples taken. The samples were stored on ice before prompt transfer to the -80°C freezer in the laboratory.

Subgingival plaque collection

Ten periodontal pockets (PPD ≥ 5 mm) were identified and recorded in the CRF. Any supragingival plaque was removed with curettes and cotton pellets. Sterile endodontic paper points (up to three, parallel, size 60) were inserted into each periodontal pockets for 10 seconds. The points were immediately transferred to sterile, dry microcentrifuge tubes. Any excessively blood-soaked points were discarded and new samples taken. The samples were placed on ice immediately before prompt transfer to storage at -80°C.

3.4.15 ***Follow-up***

Participants were scheduled to return for their study assessments at three time points: visit 4 (4 weeks post-randomisation, minus 3 days or plus 14 days), visit 5 (3 months post randomisation, minus 15 days or plus 28 days), visit 6 (6 months post-randomisation, minus 15 days or plus 28 days). The 4-week and 6-month time points and associated visit windows were based upon the Russell Standards for smoking cessation studies (West *et al.*, 2005b). Participants could withdraw from the study for any reason, at any time; for those who withdrew, no further data or tissue were collected post-withdrawal and no other research procedures were carried out on or in relation to the participant. Participants who failed to attend a scheduled visit and were unreachable were deemed lost to follow-up. Since the interventions were delivered at the start of the study it was almost impossible to withdraw from just the intervention and continue follow-up.

3.4.16 ***Safety/adverse events***

Participant safety was monitored from the time each participant signed an informed consent form until conclusion of the study. The sponsor's standard operating procedure (SOP) on managing adverse events was followed (Newcastle Joint Research Office, 2015; Newcastle Joint Research Office, 2017).

Adverse Events (AE): At the time of enrolment, a medical history was recorded. At all subsequent time points, AEs were detailed in the CRF. The chief investigator made an assessment of the relationship of the event to the study (i.e. 'definitely not related', 'probably not related', 'possibly related', 'probably related', 'definitely related') and of expectedness as per available reference safety information for e-cigarettes.

Serious Adverse Events (SAE): Any serious adverse event (SAE) as defined by the International Council for Harmonisation (ICH) Guideline for Good Clinical Practice E6, were reported to the REC by the chief investigator.

3.4.17 *Approvals and monitoring*

Newcastle upon Tyne Foundation Hospital Trust (NuTH) acted as the sponsor for this study. A favourable opinion was obtained from the North East- Tyne & Wear South NHS Research Ethics Committee on 03/08/2016 with the reference number 16/NE/0219. The Health Research Authority (HRA) approved the project and subsequent amendments (Integrated Research Approval System [IRAS] project ID: 199724). Details of the amendments are provided in Table 3.12.

A Trial Oversight Committee (TOC) was responsible for data and patient safety monitoring. The TOC combined the roles of a Trial Steering Committee and Data Monitoring Committee. The TOC was an independent group of experts consisting of a periodontal research expert, statistician and two lay members. A TOC charter was created at the first meeting (see Appendix Q) with subsequent meetings at 4, 7, 10, 13, 18 and 24 months.

Protocol version	Amendment	Details	Approved Date
1.0, dated 30/07/2016	Original submission		REC: 03/08/2016
1.1, dated 24/08/2016	Protocol changes	Non-substantial changes were made to the protocol following REC approval. This was to confirm who would have access to data and update the sponsor contact details.	HRA: 02/09/2016 Notified REC: 06/09/2016
1.2, dated 13/10/2016	Protocol changes	Non-substantial changes were made to the protocol. Change in the way periodontitis was classified and several minor administrative changes. The classification changes comprised the removal of the BOP criterion as it was proving to be an unreliable index to use in smokers (smoke affects the periodontal vasculature making this hard to interpret). Additionally the term 'sites' was used instead of 'teeth' in order to aid recruitment to this feasibility study.	HRA: 4/11/16
1.2, dated 13/10/2016	Addition of PICs	Submitted as a 'substantial amendment' but downgraded by the HRA to a non-substantial amendment (Category B).	HRA: 4/11/16 Sponsor sign off: 9/11/2016
1.3, dated 06/04/2017	Protocol changes and use of promotional materials	Non-substantial changes were made to the protocol. The minimum number of teeth required was reduced from 20 to 16 (16 teeth represents 50% of the dentition of a normal adult). Promotional materials were developed to enhance recruitment as existing recruitment centres.	HRA: 09/05/2017
1.3, dated 06/04/2017	Extension of study end date	Non-substantial amendment to extend the recruitment period and study end date by 4 months.	Sponsor sign off: 21/07/2017

Protocol version	Amendment	Details	Approved Date
		Original recruitment end date: 20/09/2017. Amended recruitment end date: 20/01/2018 Original study end date: 31/03/2018 Amended study end date: 31/07/2018	HRA approval: 27/07/2017

Table 3.12 Protocol approval and amendment dates.

3.4.18 *Registration and funding*

This study was accepted for adoption to the NIHR portfolio on 12th September 2016 and registered on the International Standard Randomised Controlled Trial Number (ISRCTN) registry (ISRCTN17731903) on 19th September 2016.

A full version of the protocol is provided in Appendix R.

This study was funded by a NIHR Doctoral Research Fellowship (DRF-2015-08-077).

3.4.19 *Data management and confidentiality*

All study-related information was stored securely at the DCRF. All identifiable participant information, including signed consent forms, was stored in locked filing cabinets in the restricted access DCRF office. Paper-based CRFs were used for the collection of clinical data, with blinded and un-blinded versions of the CRF for each participant. The CRFs were identified by a coded ID number and participant initials. All records that contained names or other personal identifiers, such as informed consent forms, were stored separately from those study records which were identified by code number only. Only investigators had access to information linking the participants to the ID numbers.

During data collection any modification to a written form or source document was amended with a single line through the erroneous data, with the correction legibly entered, as well as the initials and date of the person making the correction. Data were entered into secured databases (IBM SPSS Statistics, Version 24, Chicago, SPSS Inc.), password protected on the Newcastle University server. Source documents used to originally record participant data were maintained as part of standard case notes in the NDH.

3.4.20 *Missing data*

Smoking outcome data

Those who did not attend for review visits when smoking outcome data were collected (visits 4, 5 and 6) were considered as continuing smokers or to have relapsed, in line with standard research practice (West *et al.*, 2005b; Hartmann-Boyce *et al.*, 2016). Therefore, missing data were recorded as non-quitters for the outcomes: self-reported quitters, RS6-eCO, RS6-S. For continuous data (eCO, SC, SA), missing data were not imputed.

Periodontal data

Missing periodontal data due to participant loss to follow-up were not imputed.

Teeth lost during the study

Several of the oral health outcome measures for this study were 'summary' measures calculated on all teeth present. Teeth that were planned to be removed as part of the initial treatment plan were not included in any analysis and periodontal indices were not collected on such teeth. For teeth that were lost during the study period (i.e. their loss was not in the initial treatment plan) a 'last observation carried forwards' approach was used for the periodontal indices where possible i.e. if a tooth was lost between visit 5 and 6 then the data were carried forwards from visit 5. If a tooth was lost before visit 5 then no data were imputed.

Questionnaires

For missing questionnaire (OHQoL-UK, FTND, MPSS) data, published guidelines were followed for validated questionnaires. If no such guidelines were available, the 'rule of halves' was employed (Fairclough and Cella, 1996; Fayers *et al.*, 1998; Peyre *et al.*, 2011). For the OHQoL-UK questionnaire, patients who had not responded to ≥10% of the items in OHQoL-UK questionnaire were excluded from analyses, with their responses being treated as missing data. For patients who had <10% missing responses, the answers to the missing items were derived using group mean score imputation for each item in order to calculate the individual domain scores and the summary scores as reported in the literature (Steele *et al.*, 2004; Durham *et al.*, 2013; Irani *et al.*, 2015). For the FTND and MPSS questionnaires no published guidelines exist on how to manage incomplete data and the 'rule of halves' was used (missing item replaced with the mean of the answered items in the subscale, if at least half of the subscale has been answered).

3.4.21 ***Statistics***

In accordance with recommendations for the analysis of feasibility studies, the data analyses were descriptive and statistical comparisons between the randomised groups were not undertaken. For the feasibility outcome measures all proportions/rates were calculated as defined and reported with 95% confidence intervals (CIs). Summaries of the change from baseline to 3 months and baseline to 6 months for the study assessment outcome measures were reported as: minimum value, median (lower quartile [LQ]- upper quartile [UQ]), mean (standard deviation, SD), maximum value and 95% CI.

3.5 **Results**

The following section describes the results for the quantitative aspects of the feasibility study. Chapters 4 and 5 cover the qualitative findings (derived from participant interviews) as well as the feasibility aspects of the e-cigarette intervention.

3.5.1 ***Study set-up***

The primary objective of this pilot RCT was to assess the viability of delivering and evaluating an e-cigarette intervention within a research study. Given the unusual situation of e-cigarettes and their regulatory status, the study set-up was complicated and formed an important feasibility component of the study.

A research study which provides a medicinal product to a participant to investigate a medical claim is categorised as a Clinical Trial of Investigational Medical Product (CTIMP). CTIMPs require clinical trial authorisation (CTA) which is granted by the MHRA. The authorisation requirements vary depending on the risk of the study. Prior to April 2015 there were 13 UK e-cigarette clinical studies registered on clinical research trial databases (Clinicaltrials.gov, EudraCT database and the UK Clinical Trials Gateway), which were all classed as non-CTIMPs (to the best of our knowledge). Subsequently, there was an 18-month period in which no new trials were registered (until this pilot RCT in September 2016). Although e-cigarette regulations were established following the implementation of the EU TPD, there was still uncertainty about research regulations. In the case of our study, the MHRA initially categorised it as a CTIMP requiring CTA (a change from the previous studies), before downgrading the study to a non-CTIMP due to its feasibility outcomes. However, I continued to investigate the regulatory challenges as they could potentially impede a future definitive trial.

As previously mentioned, authorisation requirements vary depending on the risk of the study. There are different levels of CTIMPs:

- Type A- Comparable to the risk of standard medical care
- Type B- Somewhat higher than the risk of standard medical care
- Type C- Markedly higher than the risk of standard medical care

Type A studies are much less burdensome in terms of obtaining authorisation and conducting the trial, as they are considered to be low-risk. An example of a type A study would be a study using a product that already has a medicinal licence for the indication in question. These

products will have 'Summary of Product Characteristics' documents in the public domain, which could be submitted to the MHRA, without any interaction with the manufacturer.

However, as no medically licenced e-cigarette product is yet available, it is likely that studies will classed as type B or C CTIMPs (this stance changed in 2017, which is discussed at the end of this section). These higher risk studies require more detailed information as part of the authorisation process. This includes the production of an Investigational Medicinal Product Dossier (IMPD) and Investigator Brochure which are substantial documents that require significant input from the Investigational Medicinal Product (IMP) manufacturer. They set out details of the manufacture of the product and contain important safety information.

Within the e-cigarette market, the only manufacturers with large enough research & development departments to be able to provide the level of information required are likely to be those larger brands owned by tobacco companies. This poses a barrier for any university-based researcher as non-disclosure agreements (NDAs) would need to be put in place and many universities would not allow this. Within Newcastle University I explored the feasibility of setting up these NDAs with the business development team (with input from the university faculty steering group) and it was concluded that the university would be unlikely to sign such a NDA, or at the very least, it would require significant amounts of legal input. Therefore, at the time, conducting a clinical trial on e-cigarettes in the UK would be almost impossible for a university-based researcher.

I was subsequently invited to join colleagues, led by ASH, to work with the MHRA in establishing a suitable solution. They have subsequently agreed that a clinical trial using a TPD regulated e-cigarette (all those available for general sale in the UK) would not be categorised as a CTIMP and hence not need CTA, avoiding the aforementioned barriers (Medicines and Healthcare products Regulatory Agency, 2017). If the trial included medicinal products (such as nicotine patches) then the study would be classed as a CTIMP and require CTA.

3.5.2 *Participant recruitment*

This study aimed to recruit 80 participants over a 12-month period (7 participants/month). By 12 months, 66 participants had been recruited and the recruitment period was extended by three months. Recruitment opened on 20th September 2016 and closed on 7th December 2017 when the eightieth participant was recruited. Data collection was completed on 7th June 2018, when the last patient visit occurred. The majority of the patients were recruited from the clinics of the NDH, mainly through periodontal new patient clinics or the DEC.

Table 3.13 shows the detailed breakdown of the recruitment source. PICs identified a large number of potentially eligible participants but less than half of these progressed into the study, contributing 15 in total. The overall consent rate was 67% [95% CI: 58%-75%] of those eligible, but this masked differences between NDH clinics and PICs of 77% [95% CI: 28%-59%] and 43% [95% CI: 67%-85%] respectively. Figure 3.5 shows the CONSORT flow diagram.

Recruitment source	Potentially eligible participants [n (%)]	Consented and randomised [n (%)]
Periodontal new patient clinic	29 (24%)	24 (30%)
Other new patient clinics	9 (8%)	9 (11%)
Dental Emergency Clinic (DEC)	43 (36%)	29 (36%)
Participant Identification Centres (PICs)	35 (29%)	15 (19%)
Other e.g. Undergraduate student clinic	3 (3%)	3 (4%)
Total	119 (100%)	80 (100%)

Table 3.13 Recruitment source of study participants.

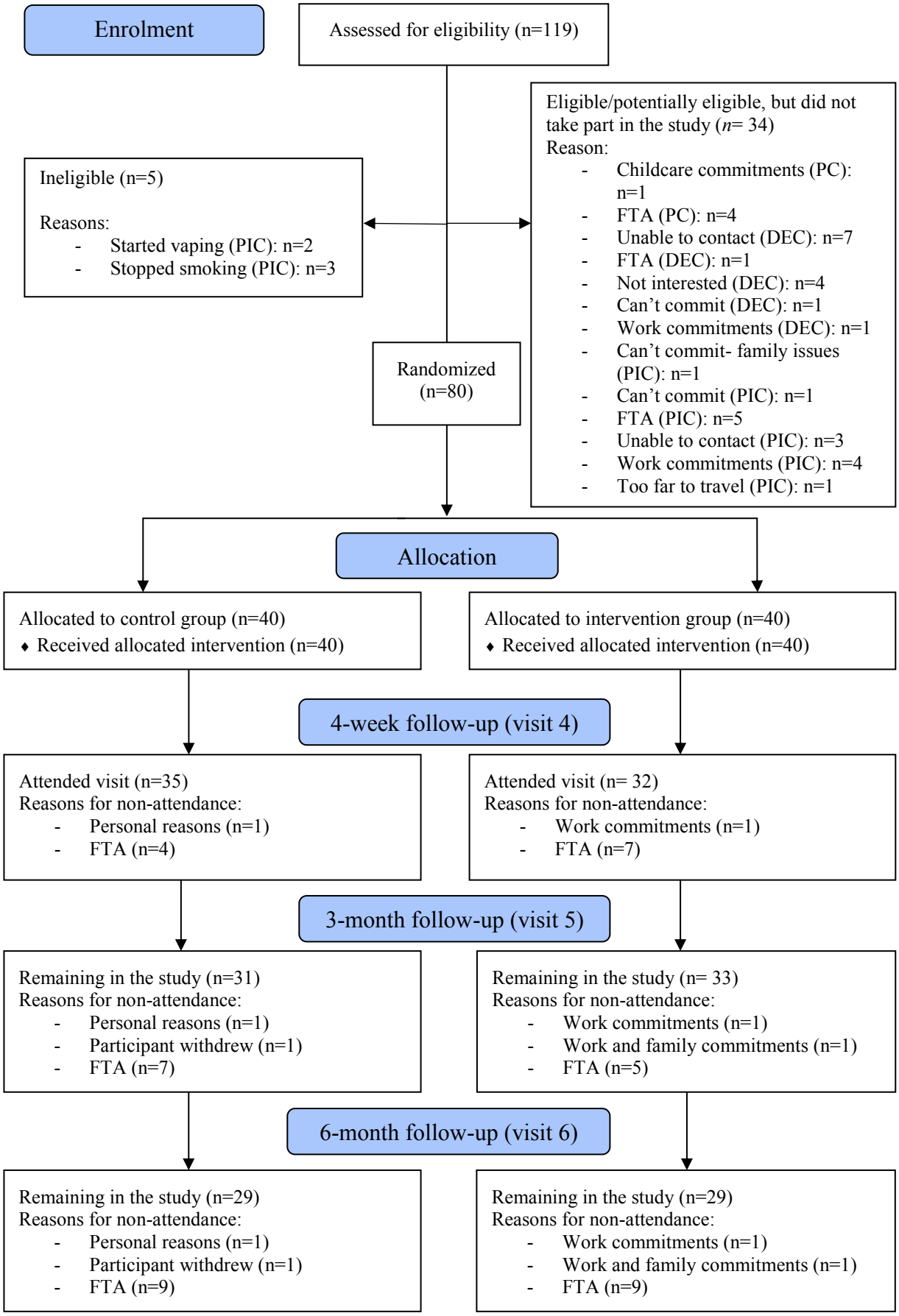

Figure 3.5 CONSORT flow diagram.

PC= Periodontal new patient clinic, DEC= Dental emergency clinic, PIC= Participant Identifying Centre, FTA= Failed to attend.

3.5.3 ***Eligibility rates***

One of the trial objectives was to estimate eligibility rates among the patient population. Due to the wide range of recruitment sources, it was not possible to collect the relevant data (i.e. the magnitude of the denominator) to estimate the eligibility rate from the whole patient population. However, it was possible to estimate the eligibility rate from the periodontal new patient clinic. Twenty-nine eligible participants were identified from 391 patients giving a 7.4% eligibility rate [95% CI: 5.2%-10.5%]. Reasons for ineligibility from the periodontal new patient clinic are provided in Table 3.14.

Eligibility outcome	No. of patients
Eligible	29 (7.4%)
Ineligible	362 (92.6%)
Reason for ineligibility:	
Non-smoker	334 (85.4%)
Smoker but smokes <10 factory-made cigarettes/day	8 (2.0%)
Using an e-cigarette (3 or more days use in the last 30)	8 (2.0%)
<16 natural teeth[#]	4 (1.0%)
Declined participation in research study*	4 (1.0%)
Periodontitis does not meet criteria	2 (0.5%)
Significant medical history	1 (0.3%)
Currently undergoing extensive dental, orthodontic, implant or peri-implant treatment	1 (0.3%)
Pregnant/nursing	0
Periodontal treatment (other than scale and polish) in last 6 months	0

Table 3.14 Eligibility outcomes from the periodontal new patient clinic.

This was 20 teeth for the first part of the study until the protocol change after seven months.

*Declined to take part in research study at the initial contact by the usual care team.

3.5.4 ***Participant follow-up***

Participants were scheduled to return for their study assessments at the following time points:

- Visit 4: 4 weeks post-randomisation (minus 3 days or plus 14 days)
- Visit 5: 3 months post-randomisation (minus 15 days or plus 28 days)
- Visit 6: 6 months post randomisation (minus 15 days or plus 28 days)

The study window periods for visits 4 and 6 were based on the Russell Standards for smoking cessation studies (West *et al.*, 2005b). Four participants withdrew from the study and 18 participants were lost to follow up. The most frequent time point for withdrawal/lost to follow-up was after visit 3; Table 3.15 provides a detailed breakdown. Fifty eight (73%) participants attended visit 4 within the designated study window, two (3%) attended early, seven (9%) attended late and 13 (16%) did not attend. Fifty nine (74%) participants attended visit 5 within the designated study window, five (6%) attended early, three (4%) attended late and 16 (20%) did not attend. Fifty one (64%) participants attended visit 6 within the designated study window, two (3%) attended early, five (6%) attended late and 22 (28%) did not attend. A detailed breakdown of participant follow-up, by randomisation group, is provided in Table 3.16 and Figure 3.6. There were no differences in the numbers of participants attending each visit by randomisation group and only minor differences in the proportion attending within the designated visit window. At the final data collection point (6 months), 11 participants in each randomisation group did not attend, giving 58 participants for the final analysis. The baseline readings of key parameters are presented in Table 3.20. Those participants lost to follow-up appeared to have higher eCO and FTND readings and more severe periodontal diseases.

Participant No.	Study Arm	Study visits completed?	Reason
1004	Intervention	1,2 (3 not required)	Work commitments
1014	Control	1,2,3,4,5	FTA/unreachable
1019	Control	1,2,3,4	FTA/unreachable
1020	Intervention	1,2,3,4	Work and family commitments
1021	Control	1,2,3	Personal reasons
1022	Control	1,2,3,4	FTA/unreachable
1030	Intervention	1,2,3	FTA/unreachable
1031	Control	1	FTA/unreachable
1032	Intervention	1,2,3,4,5	FTA/unreachable
1033	Intervention	1	FTA/unreachable
1037	Control	1,2,3,4	Subject decision
1038	Control	1	FTA/unreachable
1039	Intervention	1	FTA/unreachable
1046	Control	1,2,3	FTA/unreachable
1056	Intervention	1,2,3	FTA/unreachable
1057	Intervention	1,2,3	FTA/unreachable
1058	Intervention	1,2,5	FTA/unreachable
1060	Control	1,2,3,4	FTA/unreachable
1064	Control	1,2,3	FTA/unreachable
1068	Intervention	1,2,3,4,5	FTA/unreachable
1073	Control	1,2,3,4,5	FTA/unreachable
1079	Intervention	1,2,3,4,5	FTA/unreachable
1048	Intervention	1,2,5,6	FTA/unreachable for visit 3&4 but attended visit 5 & 6.

Table 3.15 Details of withdrawals and loss to follow-up.

FTA= Failed to attend

		Control n=40	Intervention n=40	Total n=80
Visit 1 (Baseline)		40 (100%)	40 (100%)	80 (100%)
Visit 4	Complied with study window	29 (73%)	29 (73%)	58 (73%)
(4 weeks [minus 3 days or plus 14 days])	Outwith study window	6 (15%)	3 (8%)	9 (11%)
	Did not attend	5 (13%)	8 (20%)	13 (16%)
Visit 5	Complied with study window	28 (70%)	31 (78%)	59 (74%)
(3 months [minus 15 days or plus 28 days])	Outwith study window	3 (8%)	2 (5%)	5 (6%)
	Did not attend	9 (23%)	7 (18%)	16 (20%)
Visit 6	Complied with study window	27 (68%)	24 (60%)	51 (64%)
(6 months [minus 15 days or plus 28 days])	Outwith study window	2 (5%)	5 (13%)	7 (9%)
	Did not attend	11 (28%)	11 (28%)	22 28%)

Table 3.16 Participant follow-up by randomisation group.

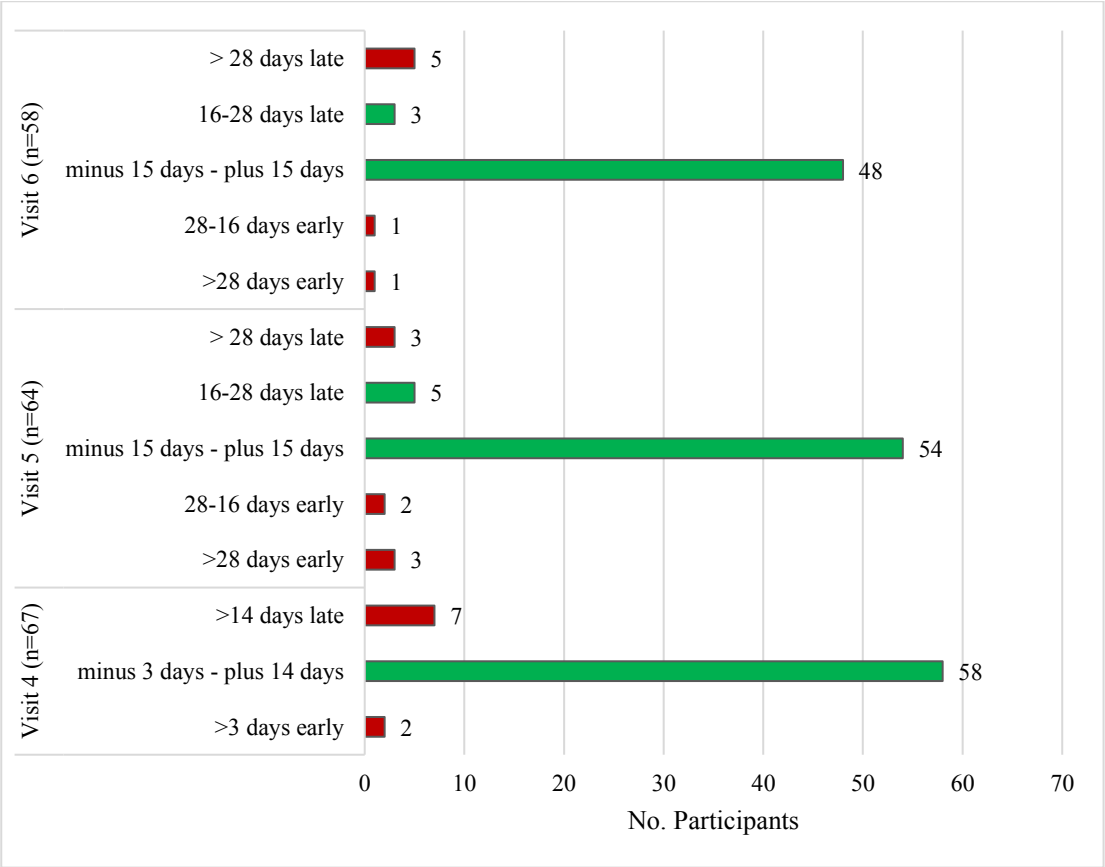

Figure 3.6 Compliance with study windows at visit 4, 5, and 6.

Green bars show those who attended within visit window.

3.5.5 *Baseline participant characteristics*

The study sample comprised 38 (47.5%) males and 42 (52.5%) females. Ethnicity was primarily white (n=75, 94%) (British, Irish or other white) with five (6%) Asian or Asian British, reflective of the North East's population (Office of National Statistics, 2018a). The majority of the participants were in employment (n=60, 75%) mainly working in routine or manual (n=20, 25%) or in intermediate (n=22, 27.5%) occupations. There was a good balance with respect to all demographic characteristics which are presented by randomisation group in Table 3.17.

The age of the participants ranged from 19 to 71 years at the time of randomisation. The mean age of the participants was 44 years. Fifty eight (73%) reported smoking factory cigarettes, 21 (13%) reported smoking hand-rolled cigarettes and one (1%) reported smoking both. The mean number of cigarettes smoked per day was 17, 16 and 21, respectively for all, factory and hard-rolled cigarettes. The majority of participants reported started smoking in their teenage years, with a mean age of 16 years. The mean baseline eCO reading was 21 ppm with all but one participants scoring a reading >10 ppm, indicating they were current tobacco smokers (one participant had refrained from smoking prior to the baseline visit and hence provided a eCO reading of 1 ppm). The participants had a moderate nicotine dependence with a mean FTND score at baseline of 5.0. There was a good balance with respect to all age and smoking behaviour demographics which are presented by randomisation group in Table 3.18.

The number of teeth (excluding third molars) that participants had at baseline ranged from 16 to 28, with a mean of 24 and a median of 25. The participants demonstrated a severe level of periodontal disease, in keeping with the study inclusion criteria. The mean PPD was 4.0 mm with the mean percentage of sites with PPDs ≥5 mm being 40%. The mean percentage BOP was 20%. A low-moderate amount of xerostomia was observed with a mean CODS of 4.0, indicating some reduced mucosal wetness. The descriptive statistics of the baseline oral health outcome measures are presented in Table 3.19. Many of the measures demonstrated good balance across randomisation group (No. teeth, MGI, PPD, CAL, PESA, CODS, OHQoL-UK) but overall there was a tendency for the severity of the periodontal disease to be worse in the control group, specifically: PPD, percentage sites with PPD ≥5 mm, percentage sites with PPD ≥6 mm, PI, BOP, PISA.

For those participants who were lost to follow-up, key parameters are presented in Table 3.20. Those participants lost to follow-up appeared to have higher eCO and FTND readings and more severe periodontal diseases.

Categorical Baseline Characteristic [n (%)]	Control group n=40	Intervention group n=40	Total n=80
Sex			
Female	20 (50%)	22 (55%)	42 (52.5%)
Male	20 (50%)	18 (45%)	38 (47.5%)
Ethnicity			
White (British, Irish, other White)	36 (90%)	39 (97.5%)	75 (93.8%)
Mixed (White & Black Caribbean, White & Black African, White & Asian, other Mixed)	0	0	0
Asian or Asian British (Indian, Pakistani, Bangladeshi, other Asian)	4 (10%)	1 (2.5%)	5 (6.3%)
Black or Black British (Caribbean, African, other Black)	0	0	0
Chinese or other ethnic group	0	0	0
Not Stated	0	0	0
Occupation			
Working in a routine or manual occupation	9 (22.5%)	11 (27.5%)	20 (25%)
Working in an intermediate occupation	9 (22.5%)	13 (32.5%)	22 (27.5%)
Working in a managerial or professional occupation	9 (22.5%)	9 (22.5%)	18 (22.5%)
Unemployed/not working for a year or more	6 (15%)	2 (5%)	8 (10%)
Full time student	0	1 (2.5%)	1 (1.3%)
Retired	1 (2.5%)	4 (10%)	5 (6.3%)

Categorical Baseline Characteristic [n (%)]	Control group n=40	Intervention group n=40	Total n=80
Sick/Disabled/Unable to return to work	4 (10%)	0	4 (5.0%)
Home carer (unpaid)	2 (5%)	0	2 (2.5%)
None of these	0	0	0

Table 3.17 Baseline categorical demographic characteristics.

Continuous Baseline Characteristic		Control group		Intervention group	Total
Min **Median (LQ-UQ)** **Mean (SD)** **Max**		**n=40**		**n=40**	**n=80**
Age [years]		25 44 (38-52) 45 (9.5) 61		19 43 (35-52) 45 (11.8) 71	19 43 (37-52) 44.3 (10.7) 71
Number of cigarettes/day [any]		10 15 (11-20) 17 (7.0) 30		10 15 (15-20) 17 (6.4) 40	10 15 (13-20) 17.4 (6.6) 40
Number of factory cigarettes/day	n=33	5 15 (10-20) 16.6 (7.2) 30	n=26	10 15 (10-20) 14.8 (4.4) 25	5 15 (10-20) 15.8 (6.1) 30
Number of hand-rolled cigarettes/day	n=8	12 15 (15-28) 19 (7.1) 30	n=14	15 20 (19-26) 22 (7.0) 40	12 20 (15-26) 21 (7.0) 40
Age started smoking		10 16 (15-18) 16 (2.8) 24		10 15 (14-16) 15 (3.2) 29	10 15 (14-17) 15.7 (3.0) 29

Continuous Baseline Characteristic	Control group	Intervention group	Total
Min **Median (LQ-UQ)** **Mean (SD)** **Max**	**n=40**	**n=40**	**n=80**
eCO [ppm]	1 18 (10-26) 18 (10.0) 49	6 22 (12-32) 23 (12.2) 55	1 19.5 (12-28) 20.6 (11.3) 55
FTND	1 5 (3-7) 5 (2.4) 9	1 5 (4-6) 5 (1.8) 9	1 5 (3-7) 5 (2.1) 9
MPSS	14 21 (18-27) 23 (7.0) 44	13 22 (19-26) 23 (5.9) 40	13 21 (18-27) 23 (6.4) 44
SC (ng/ml)	0 322 (203-382) 303 (128.3) 541	133 310 (265-433) 343 (138.1) 754	0 314 (249-409) 323 (134.0) 754
SA (ng/ml)	0 0.7 (0.2-1.7) 1.1 (1.4)	0.1 0.9 (0.5-1.3) 1.2 (1.2)	0 0.7 (0.4-1.4) 1.2 (1.3)

Continuous Baseline Characteristic	Control group	Intervention group	Total
Min	**n=40**	**n=40**	**n=80**
Median (LQ-UQ)			
Mean (SD)			
Max			
	7.3	5.4	7.3

Table 3.18 Descriptive statistics of age and smoking demographics at baseline by randomisation group.

Clinical Examination **Min** **Median (LQ-UQ)** **Mean (SD)** **Max**	**Control group** **n=40**	**Intervention group** **n=40**	**Total** **n=80**
Number of teeth (excluding 3rd molars)	16 25 (21-27) 24 (3.6) 28	16 25 (20-27) 24 (4.0) 28	16 25 (21-27) 24 (3.8) 28
Mean PI	0.1 1.1 (0.5-1.6) 1.1(0.7) 2.4	0.0 0.6 (0.3-1.3) 0.8 (0.6) 2.4	0.0 0.9 (0.4-1.5) 1.0 (0.7) 2.4
% BOP score	1 19 (7-37) 24 (18.3) 68	0 13 (5-25) 16 (13.4) 54	0 16 (6-31) 20 (16.4) 68
Mean MGI	1 2.6 (2.3-2.8) 2.5 (0.5) 3.4	1.6 2.4 (2.1-2.8) 2.5 (0.4) 3.3	1.0 2.5 (2.2-2.8) 2.5 (0.5) 3.4
Mean PPD [mm]	2.6 4.1 (3.7-4.5) 4.1 (0.8) 6.4	2.5 3.9 (3.4-4.3) 3.9 (0.7) 6.0	2.5 3.9 (3.5-4.4) 4.0 (0.7) 6.4

Clinical Examination	Control group	Intervention group	Total
Min **Median (LQ-UQ)** **Mean (SD)** **Max**	**n=40**	**n=40**	**n=80**
Mean CAL [mm]	2.7 4.9 (4.3-6.1) 5.2 (1.4) 8.5	3.0 5.0 (4.1- 6.0) 5.1 (1.3) 7.7	2.7 5.0 (4.2-6.0) 5.1 (1.3) 8.5
PESA [mm^2]	1241 1971 (1582-2837) 2134 (667) 3648	929 1944 (1512-2383) 2014 (644) 4008	929 1959 (1568-2484) 2074 (654) 4009
PISA [mm^2]	10 378 (140-1159) 635 (630) 2141	0 266 (104-589) 387 (346) 1333	0 351 (128-731) 511 (520) 2141
No. of sites with PPD ≥5 mm	11 62 (38-81) 61 (30.9) 136	11 49 (34-79) 54 (27.5) 123	11 57 (37-80) 57 (29) 136
% of sites with PPD ≥5 mm	7 44 (29-55) 42 (19.6)	7 39 (25-53) 38 (18.1)	7 40 (27-53) 40 (18.8)

Clinical Examination	Control group	Intervention group	Total
Min **Median (LQ-UQ)** **Mean (SD)** **Max**	**n=40**	**n=40**	**n=80**
	91	74	91
No. of sites with PPD ≤4 mm	20	28	20
	79 (60-100)	86 (65-107)	81 (62-105)
	83 (32.1)	87 (30.3)	85 (31)
	157	151	157
% of sites with PPD ≤4 mm	13	20	13
	56 (45-71)	62 (47-75)	60 (47-74)
	58 (19.4)	61 (19.1)	59 (19)
	94	93	94
CODS	0	2	0
	4 (3-5)	4 (3-5)	4 (3-5)
	4 (1.3)	4 (1.0)	4 (1.2)
	6	7	7
OHQoL-UK	32	25	25
	42 (40-45)	44 (40-47)	43 (40-47)
	43 (6.6)	44 (8.7)	43 (7.7)
	66	65	66

Table 3.19 Descriptive statistics of baseline oral health outcome measures by randomisation group.

Baseline variable	All participants		Participant lost to follow-up		Remaining participants	
	Control group n=40	Intervention group n=40	Control group n=11	Intervention group n=11	Control group n=29	Intervention group n=29
Mean age (SD)	45 (9.5)	45 (11.8)	48 (6.4)	37 (12.8)	43 (10.3)	47 (10.5)
Mean eCO (SD)	18 (9.9)	23 (12.2)	21 (8.1)	26 (10.7)	17 (10.4)	22 (12.8)
Mean self-reported cigarettes/day (SD)	17 (6.9)	17 (6.4)	18 (4.8)	16 (4.4)	17 (7.6)	21 (9.0)
Mean FTND (SD)	5 (2.4)	5 (1.8)	6 (2.1)	6 (2.1)	5 (2.4)	5 (1.6)
Mean PPD (SD)	4.1 (0.7)	3.9 (0.7)	4.4 (0.4)	4.1 (0.6)	4.0 (0.8)	3.8 (0.7)
Mean No. teeth (SD)	24 (3.6)	24 (4.0)	21 (3.6)	24 (3.9)	25 (3.0)	24 (4.1)
Mean % sites with PPD ≥5 mm (SD)	42 (19.6)	38 (18.1)	50 (13.3)	47 (20.5)	39 (20.8)	35 (16.2)

Table 3.20 Baseline characteristics by lost to follow-up.

3.5.6 *Safety data*

There were no SAEs in this study but 56 AEs were observed across 35 patients. The most frequently reported AEs were: toothache (15 events in 13 participants), dentine hypersensitivity (6 events), tooth/teeth loss (5 events), dental/periodontal abscess (5 events), and fractured/carious filling or tooth (5 events). Seven participants had unplanned tooth extractions during the study period, losing a total of 15 teeth. Two participants reported mouth ulceration and three separate participants reported soreness of the intra-oral soft tissues. All five of these were in the intervention group; these symptoms are well recognised side effects of smoking cessation and NRT use. A summary of the AEs reported in this study is presented in Table 3.21.

Adverse events	Control group		Intervention group	
	No. AEs	No. of participants affected	No. AEs	No. of participants affects
Toothache	4	4	11	9
Dentine hypersensitivity	3	3	3	3
Tooth/teeth loss	5 (6 teeth)	4	5 (9 teeth)	3
Dental/periodontal abscess	2	2	3	3
Mouth ulceration	0	0	2	2
Soreness of intra-oral soft tissues	0	0	3	3
Fractured/carious filling or tooth	3	3	2	2
Other	3	2	6	5

Table 3.21 Summary of adverse events.

AEs= Adverse Events

3.5.7 *Participant compliance*

Participant compliance was determined by attendance at the review visits (visit 4, 5 and 6). Fifty seven (71%, 95% CI: 61%-80%) participants attended all of the review visits and were retained for 6-month follow-up data collection, whilst 62 (78%, 95% CI: 67%-85%) attended at least two review visits. Forty one (51%, 95% CI: 40%-62%) participants attended all of the review visits within the specified visit windows. Sixty-seven (84%, 95% CI: 74%-90%) participants were retained at the 4-week review, 64 (80%, 95% CI: 70%-87%) at the 3-month review and 58 (73%, 95% CI: 62%-81%) at the 6-month review. A summary of participant compliance with attending review visits is presented in Table 3.22. Little difference was seen between the randomisation groups but there were differences depending on recruitment source (Table 3.23).

Participants were required to complete a weekly smoking status questionnaire for the duration of the study. The majority of the participants chose to receive the weekly questionnaire by SMS text message or email (see Table 3.25). Overall, the mean number of weekly responses to the survey was 14 (95% CI: 11-17), ranging from 0 to 32 entries. For the 58 participants who completed the study, mean study duration was 29 weeks, meaning the number of questionnaire entries (per participant) should have been 29. The number of questionnaire entries, from the 58 participants who completed the study, varied from 0 to 32 with a mean of 18 (95% CI: 15-21). This was sometimes more than the 26 weeks of the study because participants started completing the questionnaire at visit 1 but week zero was designated to be at visit 2 (quit date). There was a variable amount of time between visit 1 and 2; ranging from 0 to 9 weeks, with a mean (SD) of 2.6 (2.0) weeks. Participants in the intervention group returned slightly more questionnaires than the control group. Overall, 46% of participants completed the questionnaire at least half of the time (>14 entries) and 30% completed it at least 80% of the time (>23 entries), increasing to 64% and 41% respectively, for those 59 participants who completed the study. The descriptive statistics for the completion of the weekly questionnaire are presented in Table 3.24 and Figure 3.7.

Compliance level	Randomisation group [n (%)]		
	Control group n=40	Intervention group n=40	Total n=80
All reviews	29 (73%)	28 (70%)	57 (71%)
2/3 reviews	2 (5%)	3 (8%)	5 (6%)
1/3 reviews	4 (10%)	3 (8%)	7 (9%)
0/3 reviews	5 (13%)	6 (15%)	11 (14%)

Table 3.22 Summary of participant compliance with attending follow-up visits.

Recruitment source	No. of participants attending the 6-month visit	Percentage of participants attending the 6-month visit from those recruited from source
Periodontal new patient clinic	20	83%
General restorative dentistry new patient clinic	8	89%
Dental emergency clinic	19	66%
Participant identification centre	8	53%
Other	3	100%
All	58	73%

Table 3.23 Participants attending 6-month visit by recruitment source.

Min Median (LQ-UQ) Mean (SD) Max 95% CI	Control group	Intervention group	Total
All participants	0	0	0
(n=80)	12 (3-24)	12 (2-27)	12 (3-26)
	13 (10.8)	15 (12.6)	14 (11.7)
	31	32	32
	10-16	11-19	11-17
Participants who	0	0	0
completed the study	18 (7-26)	26 (7-29)	21 (7-27)
(n=58)	16 (10.6)	19 (12.0)	18 (11.3)
	31	32	32
	12-20	15-24	15-21

Table 3.24 Descriptive statistics for the completion of the weekly smoking questionnaire (number of responses).

Contact method	No. of participants [n (%)]
SMS text message with link	66 (83)
Email with link	11 (14)
Paper version	3 (4)

Table 3.25 Preferred method of weekly smoking questionnaire.

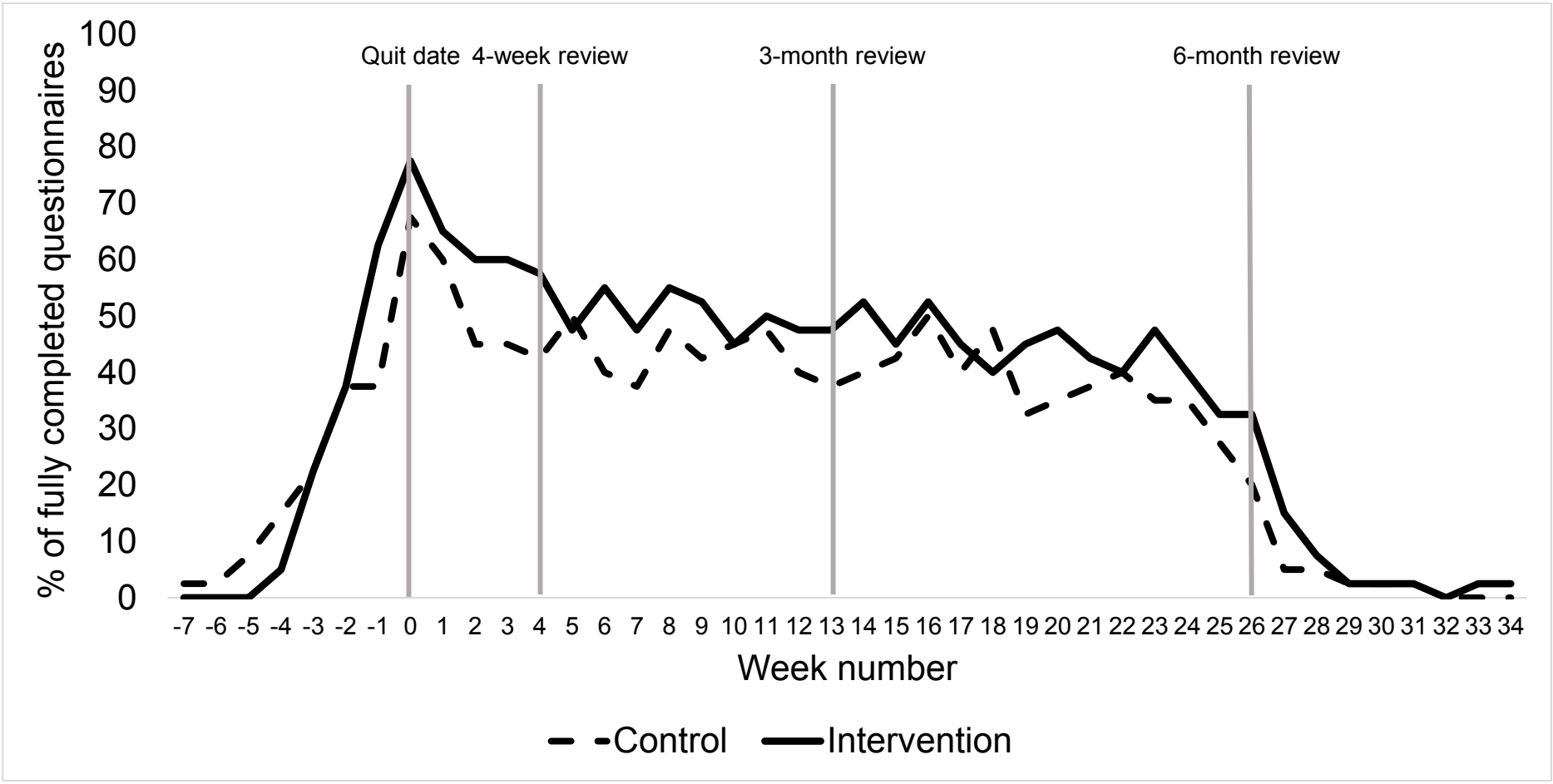

Figure 3.7 Completion of weekly smoking questionnaire by study week.

Quit date and follow-up visits illustrated on figure. Note that week zero is the quit date (visit 2). Participants were provided with the weekly questionnaire at visit 1 and there was a variable duration between visits 1 and 2, although it was recommended this was not more than 4 weeks.

3.5.8 *Intervention compliance*

The forty participants in the randomisation group were offered an e-cigarette starter kit. One participant declined the starter kit on the grounds that he did not intend to change his smoking behaviour (intention to quit was not an inclusion criteria for this study). Acceptability of the e-cigarette intervention was high with 90% of participants using the device at the quit date (visit 2). The proportion of participants still using the device remained high (>70%) at the 4-week and 3-month reviews. By the end of the study approximately half of participants were still using the e-cigarette device. Table 3.26 presents the detailed breakdown of the intervention compliance at key visits.

	Participants using e-cigarette [n (%, 95% CI)]	Participants not using e-cigarette [n (%, 95% CI)]	Participants who did not attend the visit [n (%, 95% CI)]
Visit 2 (Quit date)	36 (90%, 95% CI: 77%-96%)	2 (5%, 95% CI: 1%-17%)	2 (5%, 95% CI: 1%-17%)
Visit 4 (4 weeks)	31 (78%, 95% CI: 63%-88%)	1 (3%, 95% CI: 0%-13%)	8 (20%, 95% CI: 11%-35%)
Visit 5 (3 months)	28 (70%, 95% CI: 55%-82%)	5 (13%, 95% CI: 5%-25%)	7 (18%, 95% CI: 9%-32%)
Visit 6 (6 months)	21 (53%, 95% CI: 38%-67%)	8 (20%, 95% CI: 11%-35%)	11 (28%, 95% CI: 16%-43%)

Table 3.26 Compliance with e-cigarette usage (intervention group).

Participants were recommended to use the same brand of e-liquid as supplied in the e-cigarette starter kit. Four (10%, 95% CI: 4%-23%), six (15%, 95% CI: 7%-29%), nine (23%, 95% CI: 12%-38%) and five (13%, 95% CI: 5%-26%) participants were using another brand of e-liquid at quit date, 4 weeks, 3 months and 6 months, respectively. These other brands were: Cirro, Edge, Totally wicked, Vape 88, Vaporized, TECC and unknown non-recommended brands. Five of the six participants (83%) who achieved RS6-eCO and three of the four participants (75%) who achieved RS6-S were participants who chose to use non-recommended e-liquid brands. These 11 participants who used a non-recommended e-liquid brands on at least one time point were not obviously different with regards to age, gender and smoking behaviour. Table 3.27 provides details of those participants who chose to use non-recommended e-liquids. No information is available on the reasons why some participants chose to switch to a non-recommended brand.

Six participants reported using a different e-cigarette device (i.e. not the one supplied in the starter kit) during the study. Figure 3.8 presents the details of the devices and the time points at which they were used. Two of these participants were RS6-eCO quitters and none were RS6-S quitters.

Participant	E-liquid brand				Smoking quit status	
	Quit date	4 weeks	3 months	6 months	RS6-eCO	RS6-S
1001	Recommended	Unknown	Unknown	#	Smoker	Smoker
1003	Recommended	TECC	Totally wicked	Totally wicked	Smoker	Smoker
1013	Recommended	Recommended	Recommended	Unknown	Quitter	Quitter
1018	Recommended	Recommended	Cirro	Cirro	Quitter	Quitter
1030	VIP	*	*	*	Smoker	Smoker
1035	Recommended	Recommended	Unknown	Vaporized	Smoker	Smoker
1051	Recommended	Vaporized	Vaporized	Recommended	Quitter	Smoker
1054	Unknown	Vape 888	Vape 888	Vape 888	Quitter	Smoker
1061	Nicocig	Nicocig	Nicocig	#	Smoker	Smoker
1068	Recommended	Recommended	Unknown	*	Smoker	Smoker
1075	Edge	Edge	Edge	Recommended	Quitter	Quitter
Total using non-recommended brands (n)	4	6	9	5		

Table 3.27 Use of non-recommended e-liquids (intervention group).

Data only presented for those participants in the intervention group who reported use of non-recommended e-liquids on at least one time point. *Did not attend visit. #Stopped using a e-cigarette.

Participant	E-liquid brand				Smoking quit status	
	Quit date	4 weeks	3 months	6 months	RS6-eCO	RS6-S
1003	Recommended	TECC arc mini	TECC arc mini	TECC arc mini	Smoker	Smoker
1035	Recommended	Recommended	Unknown 3rd generation	Unknown 3rd generation	Smoker	Smoker
1051	Recommended	Recommended	PRISM T18E	PRISM T18E	Quitter	Smoker
1054	Recommended	Vype- other**	Vype-other**	Vype-other**	Quitter	Smoker
1061	Nicocig	Nicocig	Nicocig	#	Smoker	Smoker
1068	SMOCK	SMOCK	SMOCK	*	Smoker	Smoker
Total using different device (n)	2	4	6	4		

Figure 3.8 Use of different e-cigarette device (intervention group).

*Did not attend visit. #Stopped using a e-cigarette. **Participant lost their e-cigarette and tried to purchase an exact replacement of that provided in the study. The model used was no longer available and the participant purchase a newer model.

3.5.9 *E-liquid flavour and strength selection*

Those participants in the intervention group who accepted the e-cigarette starter kit had a choice of two e-liquids from four flavour options (tobacco, mint, cherry and flavourless) and four nicotine strengths (0, 6, 12, 18 mg/ml). There were ten possible e-liquid flavour selections as demonstrated in Table 3.28. The most frequent selection was tobacco and mint followed by mint only. Over half of participants (52%) did not include a tobacco flavour in their selection, while 62% included mint flavour. There were ten possible nicotine strength selections as demonstrated in Table 3.29. The most frequent nicotine strength selection was 12 mg/ml and 18 mg/ml, selected by over half of participants, while none opted for the lowest concentration options. The modal nicotine concentration was 18 mg/ml.

E-liquid selections at follow-up are presented in Table 3.30 and Table 3.31.

Flavour choice	Percentage of participants in intervention group (n=39) [% (n)]
Tobacco only	13% (5)
Cherry only	10% (4)
Mint only	21% (8)
Mint & Cherry	15% (6)
Tobacco & Cherry	5% (2)
Tobacco & Mint	23% (9)
Flavourless only	0
Flavourless & Tobacco	8% (3)
Flavourless & Mint	3% (1)
Flavourless & Cherry	3% (1)

Table 3.28 E-liquid flavour participant selection.

Nicotine choices (mg/ml)		Percentage of participants in intervention group (n=39) [% (n)]
Choice 1	Choice 2	
0	0	0
0	6	0
0	12	0
0	18	0
6	6	0
6	12	5% (2)
6	18	0
12	12	18% (7)
12	18	54% (21)
18	18	23% (9)

Table 3.29 E-liquid strength (nicotine) participant selection.

Flavour choice	Percentage of participants in intervention group [% (n)]			
	Quit date n=37	4 weeks n=30	3 months n=27	6 months n=21
Tobacco*	41% (15)	30% (9)	33% (9)	33% (7)
Mint#	38% (14)	37% (11)	30% (8)	29% (6)
Cherry	16% (6)	23% (7)	15% (4)	14% (3)
Unflavoured	3% (1)	3% (1)	4% (1)	5% (1)
Strawberry & Lime	3% (1)	3% (1)	4% (1)	
Blackcurrant		3% (1)		
Apple & Cherry			4% (1)	
Blackberry			4% (1)	5% (1)
Grape and Blackcurrant			4% (1)	
Shluuurrp			4% (1)	
Infused Vanilla				5% (1)
Strawberry Cheesecake				5% (1)
Strawberry Dream				5% (1)

Table 3.30 E-liquid flavour usage at follow-up visits.

*All tobacco flavours combined in this category. Includes 'tobacco', 'blended tobacco' and 'rolling tobacco'.
All mint flavours combined in this category. Includes: 'crisp mint', 'mint' and 'menthol'.

	Percentage of participants in intervention group [% (n)]			
	Quit date n=37	4 weeks n=30	3 months n=27	6 months n=21
Nicotine strength (mg/ml)				
18	51% (19)	40% (12)	33% (9)	29% (6)
16	5% (2)			
14		3% (1)		
12	38% (14)	43% (13)	37% (10)	38% (8)
11			7% (2)	10% (2)
10		3% (1)	4% (1)	
6	3% (1)	6% (2)	4% (1)	5% (1)
3		3% (1)	8% (2)	10% (2)
0			8% (2)	10% (2)
Can't recall	3% (1)			
Mean (SD)	15 (3.3)	14 (4.2)	12 (5.6)	11 (5.9)

Table 3.31 E-liquid strength usage at follow-up visits.

3.5.10 *E-cigarette use in the control group*

Participants in the control group were asked to use one of the traditional methods of smoking cessation in their quit attempt e.g. NRT or varenicline. They were asked to refrain from using an e-cigarette, specifically for the first four weeks but ideally over the full duration of the study. The participants in the control group were asked to sign a commitment form. Two participants declined to sign the form and one of these went on to use an e-cigarette during the study. In total, eight participants in the control group (20%, 95% CI: 11%-35%) reported using an e-cigarette at some point in the study, with one reporting usage at all post-randomisation visits. At the quit date four participants were using an e-cigarette, peaking at five participants at the 4-week and 3-month visits, and decreasing to three at the 6-month visit. Complete details are shown in Table 3.32.

Participant	Using an e-cigarette?				Smoking quit status	
	Quit date	4 weeks	3 months	6 months	RS6-eCO	RS6-S
1006	Yes	Yes	No	No	Quitter	Quitter
1008	Yes	Yes	No	No	Smoker	Smoker
1041	No	No	Yes	No	Smoker	Smoker
1063	Yes	Yes	Yes	Yes	Quitter	Smoker
1065	No	No	No	Yes	Smoker	Smoker
1067	Yes	Yes	Yes	No	Smoker	Smoker
1071	No	No	Yes	Yes	Smoker	Smoker
1078	No	Yes	Yes	No	Smoker	Smoker
Total (n)	4	5	5	3		

Table 3.32 E-cigarette use in the control group.

3.5.11 *Methods of smoking cessation (non-e-cigarette)*

A variety of smoking cessation techniques were used by our participants. Forty percent of the control group reporting making contact with the NHS stop smoking service, compared to none in the intervention group. Four of the eight participants (50%) who used an e-cigarette in the control group (see section 3.5.10) also reported making contact with the stop smoking service. Table 3.33 provides details of the smoking cessation methods reportedly used by the participants by randomisation group.

Smoking cessation method	**Randomisation group [n (%)]**		
	Control group n=40	**Intervention group n=40**	**Total n=80**
NHS stop smoking services	16 (40%)	0	16 (20%)
General Medical Practitioner (GMP) support	2 (5%)	0	2 (3%)
NRT (non-e-cigarette)	8 (20%)	4 (10%)	12 (15%)
Varenicline (Champix)	5 (13%)	0	5 (6%)

Table 3.33 Methods of smoking cessation used by randomisation group.

Some participants used multiple methods e.g. NHS stop smoking service and NRT.

3.5.12 *Oral health outcome measures*

Outcome	Control Group, n=40					Intervention Group, n=40				
Min **Median (LQ-UQ)** **Mean (SD)** **Max** **95% CI** ***Unless otherwise detailed***	**Baseline (all)**	**Baseline for those reaching 3-month visit**	**Baseline for those reaching 6-month visit**	**3 months**	**6 months**	**Baseline (all)**	**Baseline for those reaching 3-month visit**	**Baseline for those reaching 6-month visit**	**3 months**	**6 months**
Number of teeth (excluding 3rd molars)	16 25 (21-27) 24 (3.6) 28 23-25	17 26 (23-27) 25 (2.9) 28 24-26	17 26(23-27) 25 (3.0) 28 24-26	17 26 (23-27) 25 (2.9) 28 24-26	17 26 (23-27) 25 (3.0) 28 24-26	16 25 (20-27) 24 (4.0) 28 23-25	16 26 (21-27) 24 (4.0) 28 23-25	16 26 (21-27) 24 (4.1) 28 22-25	15 25 (20-27) 23 (4.4) 28 22-25	14 25 (21-27) 23 (4.5) 28 22-25
Mean PPD [mm]	2.6 4.1 (3.7-4.5) 4.1 (0.8) 6.4 3.8-4.3	2.6 4.0 (3.6-4.6) 4.0 (0.8) 6.4 3.7-4.3	2.6 3.9 (3.3-4.5) 4.0 (0.8) 6.4 3.6-4.3	2.1 3.3 (2.7-3.8) 3.3 (0.7) 4.8 3.0-3.6	2.1 3.1 (2.7-3.6) 3.3 (0.7) 4.9 3.0-3.6	2.5 3.9 (3.4-4.3) 3.9 (0.7) 6.0 3.7-4.1	2.5 3.8 (3.4-4.3) 3.9 (0.7) 6.0 3.7-4.2	2.5 3.8 (3.3-4.1) 3.8 (0.7) 6.0 3.6-4.1	2.2 3.0 (2.8-3.3) 3.1 (0.4) 4.5 2.9-3.3	2.4 3.0 (2.8-3.2) 3.0 (0.4) 4.1 2.9-3.2
Mean PPD [mm] of those sites with a baseline probing depth of ≥ 5 mm	5.0 5.6 (5.3-5.9) 5.7 (0.5) 7.3 5.5-5.8	5.0 5.5 (5.3-6.2) 5.7 (0.6) 7.3 5.5-5.9	5.0 5.5 (5.2-6.2) 5.7 (0.6) 7.3 5.5-5.9	2.6 4.2(3.2-5.0) 4.1 (1.0) 5.8 3.8-4.5	2.4 4.0 (3.2-5.0) 4.0 (1.0) 5.9 3.6-4.4	5.1 5.5 (5.2-5.9) 5.6 (0.5) 7.1 5.4-5.8	5.1 5.6 (5.2-6.0) 5.7 (0.5) 7.1 5.5-5.8	5.1 5.5 (5.2-6.0) 5.6 (0.5) 7.1 5.4-5.8	2.7 3.9 (3.6-4.3) 4.0 (0.6) 5.3 3.7-4.2	2.9 3.8 (3.4-4.3) 3.9 (0.6) 5.1 3.6-4.1
Mean PPD [mm] of those sites with a baseline probing depth of ≥ 6 mm	6.0 6.5 (6.3-7.0) 6.6 (0.4) 7.7 6.4-6.7	3.0 4.9 (4.2-5.8) 4.9 (1.0) 7.1 4.5-5.3	2.8 4.7 (3.8-5.6) 4.6 (1.1) 6.3 4.2-5.1	3.0 4.9 (4.2-6.0) 4.9 (1.0) 7.1 4.5-5.3	2.8 4.7 (4.0-6.0) 4.6 (1.1) 6.3 4.2-5.1	6.0 6.6 (6.3-7.0) 6.6 (0.5) 8.2 6.5-6.8	2.0 4.6 (4.1-5.3) 4.6 (1.0) 6.5 4.2-5.0	3.0 4.6 (3.8-5.2) 4.6 (0.9) 6.6 4.2-5.0	2.0 4.6 (4.1-5.3) 4.6 (1.0) 6.5 4.2-5.0	3.0 4.6(3.8-5.2) 4.6 (0.9) 6.6 4.2-5.0

Outcome	Control Group, n=40					Intervention Group, n=40				
Min **Median (LQ-UQ)** **Mean (SD)** **Max** **95% CI** ***Unless otherwise detailed***	**Baseline (all)**	**Baseline for those reaching 3-month visit**	**Baseline for those reaching 6-month visit**	**3 months**	**6 months**	**Baseline (all)**	**Baseline for those reaching 3-month visit**	**Baseline for those reaching 6-month visit**	**3 months**	**6 months**
Mean PPD [mm] of those sites with a baseline probing depth of ≥ 7 mm	7.0 7.3 (7.0-7.6) 7.5 (0.7) 11.0 7.2-7.7	7.0 7.3 (7.0-7.6) 7.5 (0.8) 11 7.2-7.8	7.0 7.3 (7.0-7.6) 7.5 (0.9) 11.0 7.1-7.9	3.5 5.8 (5.0-6.2) 5.6 (1.3) 10.0 5.1-6.1	2.0 5.6 (4.0-6.1) 5.1 (1.7) 10.0 4.4-5.9	7.0 7.2 (7.0-7.6) 7.4 (0.5) 8.9 7.3-7.6	7.0 7.3 (7.2-7.7) 7.5 (0.6) 8.9 7.3-7.8	7.0 7.3 (7.2-7.7) 7.5 (0.5) 8.9 7.3-7.8	0.0 4.7 (4.0-5.6) 4.8 (1.5) 8.5 4.1-5.4	0.0 4.6 (3.7-5.3) 4.4 (1.5) 6.7 3.7-5.0
Mean PPD [mm] of those sites with a baseline probing depth of ≤ 4 mm	2.4 2.8 (2.7-3.1) 2.8 (0.3) 3.5 2.8-2.9	2.4 2.8 (2.6-3.1) 2.8 (0.3) 3.5 2.7-2.9	2.4 2.8 (2.6-3.1) 2.8(0.3) 3.5 2.7-2.9	2.0 2.6 (2.4-3.0) 2.7 (0.3) 3.2 2.5-2.8	2.0 2.6 (2.4-3.0) 2.7 (0.3) 3.3 2.5-2.8	2.2 2.9 (2.7-3.0) 2.9 (0.2) 3.3 2.8-2.9	2.2 2.9 (2.7-3.0) 2.9 (0.2) 3.3 2.8-2.9	2.2 2.9 (2.7-3.0) 2.8 (0.2) 3.3 2.7-2.9	2.1 2.6 (2.4-2.8) 2.6 (0.3) 3.2 2.5-2.7	2.2 2.6 (2.4-2.8) 2.6 (2.2) 3.1 2.5-2.7
Percentage of sites with PPD ≥ 5 mm	7 44 (29-55) 42 (19.6) 91 36-48	7 41 (26-56) 41 (21) 91 33-48	7 40 (21-52) 39 (20.8) 91 31-47	0 26 (4-36) 23 (18.1) 59 16-30	0 16 (5-28) 20 (17.2) 58 13-26	7 38 (25-53) 38 (18.1) 74 33-44	7 36 (25-49) 38 (17.6) 74 32-44	7 34 (24-42) 35 (16.2) 73 29-41	2 14 (11-19) 17 (11) 52 13-21	3 13 (7-18) 14 (9.8) 46 10-17
Percentage of sites with PPD >6 mm	0 7 (1-14) 10 (11.3) 51 6-14	0 6 (1-19) 11 (12.6) 51 6-15	0 5 (1-13) 10 (12.7) 51 5-15	0 3 (0-9) 5 (6.9) 21 3-8	0 1 (0-8) 5(7.4) 28 2-8	0 6 (1-11) 8 (8.2) 37 5-10	0 6 (1-11) 8 (8.4) 37 5-11	0 5 (0-11) 7 (8.5) 37 4-10	0 1 (0-3) 2 (3.0) 15 1-3	0 1 (0-3) 2 (2.1) 8 1-3
Percentage of sites improving by ≥2 mm	-	-	-	-	2 25 (13-36) 25 (14.1) 53 19-30	-	-	-	-	7 27 (17-32) 27 (13.4) 70 21-32

Outcome Min Median (LQ-UQ) Mean (SD) Max 95% CI *Unless otherwise detailed*	Control Group, n=40					Intervention Group, n=40				
	Baseline (all)	Baseline for those reaching 3-month visit	Baseline for those reaching 6-month visit	3 months	6 months	Baseline (all)	Baseline for those reaching 3-month visit	Baseline for those reaching 6-month visit	3 months	6 months
Percentage of sites improving by ≥3 mm	-	-	-	-	2 8 (4-17) 11 (8.8) 37 8-14	-	-	-	-	0 10 (4-15) 11 (9.7) 47 7-15
Percentage of sites with baseline PPD ≥4 mm improving by ≥2 mm	-	-	-	-	20 48 (37-59) 50 (17.2) 87 43-56	-	-	-	-	22 54 (38-62) 52 (16.3) 90 46-58
Percentage of sites with baseline PPD ≥5 mm improving by ≥2 mm	-	-	-	-	22 59 (44-74) 59 (20.7) 100 51-67	-	-	-	-	11 57 (44-68) 57 (18.6) 96 50-64
Percentage of sites with baseline PPD ≥6 mm improving by ≥2 mm	-	-	-	-	0 55 (42-75) 54 (26.0) 100 44-64	-	-	-	-	0 58 (44-75) 58 (28.1) 100 47-68

Outcome	Control Group, n=40					Intervention Group, n=40				
Min **Median (LQ-UQ)** **Mean (SD)** **Max** **95% CI** ***Unless otherwise detailed***	**Baseline (all)**	**Baseline for those reaching 3-month visit**	**Baseline for those reaching 6-month visit**	**3 months**	**6 months**	**Baseline (all)**	**Baseline for those reaching 3-month visit**	**Baseline for those reaching 6-month visit**	**3 months**	**6 months**
Mean MGI	1.0 2.6 (2.3-2.8) 2.5(0.5) 3.4 2.4-2.7	1.0 2.6 (2.1-2.9) 2.5(0.5) 3.4 2.3-2.7	1.0 2.6 (2.1-2.9) 2.5 (0.5) 3.4 2.3-2.7	1.1 2.2 (1.7-2.4) 2.0 (0.4) 2.6 1.9-2.2	0.7 2.1 (1.7-2.3) 1.9 (0.5) 2.6 1.7-2.1	1.6 2.4 (2.2-2.8) 2.5 (0.4) 3.3 2.3-2.6	1.6 2.4 (2.1-2.8) 2.4 (0.4) 3.2 2.3-2.6	1.6 2.3 (2.1-2.6) 2.3(0.4) 3.1 2.2-2.5	0.8 1.8 (1.5-2.1) 1.8 (0.5) 2.8 1.7-2.0	0.7 1.7 (1.3-2.0) 1.6 (0.5) 2.6 1.4-1.8
Mean PI	0.1 1.1 (0.5-1.6) 1.1 (0.7) 2.4 0.9-1.3	0.1 1.0 (0.4-1.5) 1.0 (0.6) 2.3 0.8-1.2	0.1 1.0 (0.4-1.5) 1.0 (0.6) 2.3 0.7-1.2	0.0 3.4 (0.1-0.5) 0.4 (0.4) 1.9 0.3-0.6	0.0 3.3 (0.1-0.6) 0.4 (0.4) 1.5 0.3-0.6	0.0 0.6 (0.3-1.3) 0.8 (0.6) 2.4 0.6-1.0	0.0 0.6 (0.2-1.4) 0.8 (0.7) 2.4 0.6-1.0	0.0 0.5 (0.2-1.1) 0.7 (0.7) 2.4 0.5-1.0	0.0 0.0 0.2 (0.9-0.3) 0.3 (0.4) 1.5 0.2-0.4	0.0 0.1 (0.1-0.4) 0.4 (0.5) 1.8 0.2-0.5
Mean CAL [mm]	2.7 4.9 (4.3-6.1) 5.2 (1.4) 8.5 4.8-5.6	2.7 4.7 (4.2-5.3) 5.0 (1.4) 8.5 4.4-5.5	2.7 4.7 (4.2-5.2) 4.8 (1.2) 8.5 4.3-5.3	2.4 4.2 (3.4-5.1) 4.6 (1.6) 8.5 4.0-5.2	2.2 4.0(3.3-5.0) 4.3 (1.5) 8.2 3.8-4.9	3.0 5.0 (4.1-6.0) 5.1 (1.3) 7.7 4.7-5.5	3.3 5.1 (4.0-6.0) 5.1 (1.2) 7.7 4.7-5.6	3.3 5.0 (3.9-6.0) 5.1 (1.3) 7.7 4.6-5.6	2.8 4.9 (3.3-5.6) 4.6 (1.2) 6.6 4.1-5.0	2.8 4.4 (3.2-5.5) 4.4 (1.3) 6.7 3.9-4.9
% BOP score	1 19 (7-37) 24 (18.3) 68 18-30	2 23 (7-44) 26 (19.4) 68 19-34	2 23 (6-42) 25 (18.5) 61 18-32	1 8 (3-19) 13 (13.4) 53 8-18	0 10 (4-20) 14 (13.9) 52 9-19	0 13 (5-25) 16 (13.4) 54 12-21	0 14 (6-26) 17 (12.3) 42 12-21	0 14 (6 -29) 17(12.6) 42 12-22	0 6 (2-11) 8 (10.2) 54 5-12	0 7 (2-13) 10 (12.9) 63 5-15
CODS	0.0 4.0 (3.0-5.0) 4.0 (1.3) 6.0 3.6-4.4	0.0 4.0 (3-5) 3.8 (1.3) 6.0 3.3-4.3	0.0 4.0 (3.0-5.0) 3.7(1.3) 6.0 3.2-4.2	1.0 3.0 (2.0-5.0) 3.5 (1.4) 6.0 3.0-4.0	1.0 3.0 (2.0-4.0) 3.0 (1.4) 6.0 2.5-3.6	2.0 4.0 (3.0-5.0) 4.1 (1.0) 7.0 3.7-4.4	2 4.0 (3-4) 3.9 (0.9) 6.0 3.6-4.2	2.0 4.0 (3.0-4.0) 3.8 (0.9) 6.0 3.4-4.2	1.0 4.0 (2.0-5.0) 3.6 (1.7) 7.0 3.0-4.2	1.0 4.0 (2.0-4.0) 3.5 (1.5) 7.0 2.9-4.1

Outcome	Control Group, n=40					Intervention Group, n=40				
Min **Median (LQ-UQ)** **Mean (SD)** **Max** **95% CI** ***Unless otherwise detailed***	**Baseline (all)**	**Baseline for those reaching 3-month visit**	**Baseline for those reaching 6-month visit**	**3 months**	**6 months**	**Baseline (all)**	**Baseline for those reaching 3-month visit**	**Baseline for those reaching 6-month visit**	**3 months**	**6 months**
PESA [mm^2]	1241	1277	1277	935	874	929	929	929	809	701
	1971 (1582-2837)	2145 (1596-2958)	1979 (1589-2919)	1781 (1300-2349)	1568 (1268-2103)	1944 (1512-2383)	1956 (1552-2433)	1932 (1479-2380)	1487 (1158-1687)	1432 (1164-1641)
	2134 (667)	2241 (701)	2200 (704)	1769 (589)	1730 (599)	2014 (644)	2046 (680)	1992 (696)	1455 (393)	1423 (376)
	3648	3648	3648	2904	2903	4009	4009	4009	2612	2256
	1921-2347	1984-2498	1932-2468	1553-1985	1503-1958	1808-2220	1805-2287	1728-2257	1309-1602	1280-1566
PISA [mm^2]	10	23	1277	7	0	0	0	0	0	0
	378 (140-1159)	474 (140-1453)	1979 (133-1447)	178 (41-410)	133 (62-424)	266 (104-588)	346 (134-655)	346 (120-655)	86 (45-216)	87 (21-230)
	635 (630)	735 (677)	687 (646)	317 (396)	321 (391)	387 (346)	396 (322)	391 (324)	162 (257)	177 (265)
	2141	2141	1786	1517	1407	1333	1114	1114	1411	1332
	433-836	487-983	441-932	172-462	172-470	276-497	281-510	268-514	66-258	76-278
OHQoL-UK	32	-	32	-	30	25	-	25	-	39
	42 (40-45)		42 (40-45)		46 (42-62)	44 (40-47)		43 (41-47)		48 (46-60)
	43 (6.6)		43 (6.7)		53 (13.5)	44 (8.7)		43 (7.7)		53 (10.3)
	66		66		80	65		64		79
	41-45		41-46		47-57	41-46		40-46		49-57

Table 3.34 Oral health outcome measures.

Outcome	Control Group, n=40		Intervention Group, n=40	
Min Median (LQ-UQ) Mean (SD) Max 95% CI	**Change from baseline to 3 months**	**Change from baseline to 6 months**	**Change from baseline to 3 months**	**Change from baseline to 6 months**
Mean PPD [mm]	-1.7 -0.5 (-1.1 to -0.3) -0.7 (0.4) 0.0 -0.9 to -0.5	-1.7 -0.5 (-1.1 to -0.3) -0.7 (0.5) 0.0 -0.9 to -0.5	-2.8 -0.7 (-1.0 to -0.5) -0.8 (0.6) 0.3 -1 to -0.6	-2.7 -0.8 (-1.1 to -0.4) -0.8 (0.6) 0.0 -1.0 to -0.6
Mean PPD [mm] of those sites with a baseline probing depth of ≥5 mm	-2.4 -1.7 (-2.1 to -1.1) -1.6 (0.6) -0.6 -1.8 to -1.4	-2.6 -1.7 (-2.1 to -1.1) -1.7 (0.6) -0.4 -1.9 to -1.4	-3.6 -1.6 (-2.0 to -1.3) -1.7 (0.7) 0.1 -2.0 to -1.4	-3.8 -1.7 (-2.0 to -1.3) -1.8 (0.7) -0.9 -2.0 to -1.5
Mean PPD [mm] of those sites with a baseline probing depth of ≥6 mm	-3.4 -1.9 (-2.3 to -1.2) -1.7 (0.9) 1.1 -2.1 to -1.4	-3.5 -1.9 (-2.5 to -1.4) -1.9 (0.8) -0.2 -2.3 to -1.6	-4.4 -2.0 (-2.6 to -1.4) -2.1(1.1) 0.3 -2.5 to -1.7	-4.7 -2.0 (-2.5 to -1.7) -2.1 (1.1) 0.6 -2.5 to -1.7
Mean PPD [mm] of those sites with a baseline probing depth of ≥7 mm	-3.5 -1.9 (-2.5 to -1.1) -1.9 (0.8) -0.7 -2.2 to -1.6	-5.0 -2.2 (-3.0 to -1.4) -2.4 (1.2) -0.8 -2.9 to -1.9	-7.2 -2.7 (-3.2 to -1.9) -2.8 (1.5) 0.2 -3.4 to -2.1	-7.2 -2.6 (-4.2 to -2.0) -3.1 (1.5) -1.5 -3.8 to -2.5
Mean PPD [mm] of those sites with a baseline probing depth of ≤4 mm	-0.9 -0.1 (-0.4 to 0.1) -0.2 (0.3) 0.4 -0.3 to -0.1	-0.9 -0.1 (-0.4 to 0.2) -0.2 (0.4) 0.5 -0.3 to 0	-0.7 -0.2 (-0.3 to 0.0) -0.2 (0.3) 0.4 -0.3 to -0.1	-0.6 -0.3 (-0.5 to -0.1) -0.3 (0.3) 0.4 -0.4 to -0.2
Percentage of sites with PPD ≥5 mm	-46 -13 (-32 to -8) -17 (13.1) 1 -22 to -13	-51 -15 (-31 to -9) -19 (13) 0.5 -24 to -14	-57 -21 (-25 to -12) -21 (14.8) 10 -26 to -15	-58 -21 (-29 to -9) -22 (14) -3 -27 to -16
Percentage of sites with PPD >6 mm	-34 -3 (-7 to 0) -5 (7.6) 2 -8 to -2	-32 -3 (-8 to 0) -5 (7.0) 3 -7 to -2	-36 -4 (-7 to 0) -6 (7.8) 4 -9 to -3	-35 -3 (-7 to 0) -6 (7.9) 2 -9 to -3
Mean MGI	-1.2 -0.5 (-0.7 to -0.2) -0.5 (0.4) 0.2 -0.6 to -0.3	-1.6 -0.5 (-0.8 to -0.3) -0.5 (0.5) 0.8 -0.7 to -0.3	-1.1 -0.5 (-0.8 to -0.2) -0.5 (0.3) 0.2 -0.7 to -0.4	-1.9 -0.7 (-1.0 to -0.3) -0.7 (0.5) 1.2 -0.9 to -0.5
Mean PI	-1.4 -0.6 (-0.9 to -0.1) -0.6 (0.5) 0.3 -0.7 to -0.4	-1.5 -0.5 (-1.0 to -0.2) -0.6 (0.5) 0.4 -0.7 to -0.4	-1.6 -0.3 (-0.8 to -0.1) -0.4 (0.4) 0.1 -0.6 to -0.3	-1.6 -0.3 (-0.4 to -0.1) -0.4 (0.4) 0.2 -0.5 to -0.2
Mean CAL [mm]	-1.4 -0.4 (-1.0 to -0.1) -0.4 (0.7) 1.4 -0.6 to -0.1	-1.7 -0.4 (-1.2 to -0.2) -0.5 (0.9) 1.6 -0.8 to -0.1	-2.1 -0.6 (-0.8 to -0.3 -0.5 (0.7) 1.5 -0.8 to -0.3	-1.9 -0.7 (-1.1 to -0.2 -0.6 (0.7) 0.9 -0.9 to -0.4
% BOP score	-47 -10 (-20 to -2) -14 (14.1) 11 -19 to -8	-35 -10 (-24 to -1) -11 (13.5) 23 -16 to -6	-28 -5 (-13 to -1) -7 (11.0) 28 -11 to -3	-38 -4 (-18 to 0) -7 (13.6) 36 -12 to -2
CODS	-3 0 (-2 to 1) 0 (1.8)	-4 0 (-2 to 1) -1 (1.6)	-3 0 (-2 to 1) 0 (1.8)	-3 0 (-1 to 1) 0 (1.3)

Outcome	Control Group, n=40		Intervention Group, n=40	
Min Median (LQ-UQ) Mean (SD) Max 95% CI	Change from baseline to 3 months	Change from baseline to 6 months	Change from baseline to 3 months	Change from baseline to 6 months
	3 -0.9 to 0.4	2 -1.3 to -0.1	3 -0.9 to 0.4	2 0.8 to 0.2
PESA [mm^2]	-1240 -380 (-713 to -220) -472 (325) 1 -591 to -353	-1210 -404 (-692 to -241) -469 (320) 4 -591 to -348	-2104 -474 (-660 to -244) -541 (435) 158 -704 to -379	-2080 -457 (-786 to -237) -569 (460) 20 -744 to -394
PISA [mm^2]	-1701 -297 (-674 to -49) -418 (498) 193 -601 to -235	-1293 -238 (-712 to -48) -366 (462) 581 -541 to -190	-1032 -132 (-323 to -20) -190 (298) 626 -301 to -79	-1084 -137 (-330 to -13 -214 (332) 547 -340 to -88
OHQoL-UK	-	-24 5 (0 to 16) 9 (15.3) 47 3 to 15	-	-11 6 (0 to 16) 9 (13.2) 48 4 to 14

Table 3.35 Change in oral health outcome measures between visits.

Number of teeth

The number of teeth present at baseline ranged from 16 to 28. The distribution of the number of teeth present at baseline is presented in Figure 3.9. Fifteen teeth were lost from seven participants throughout the study, who lost between one and five teeth each. Figure 3.10 presents the number of teeth present by randomisation group at three time points.

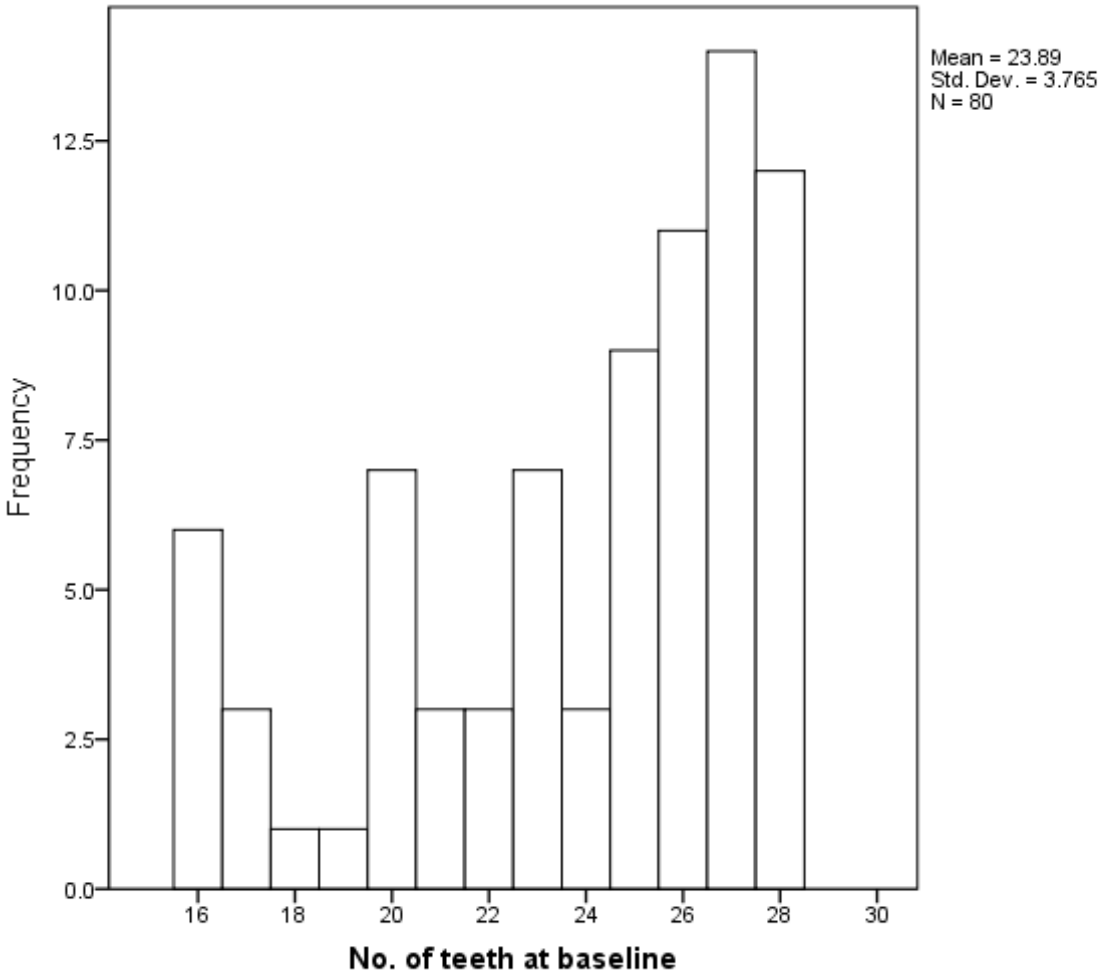

Figure 3.9 Number of teeth present at baseline.

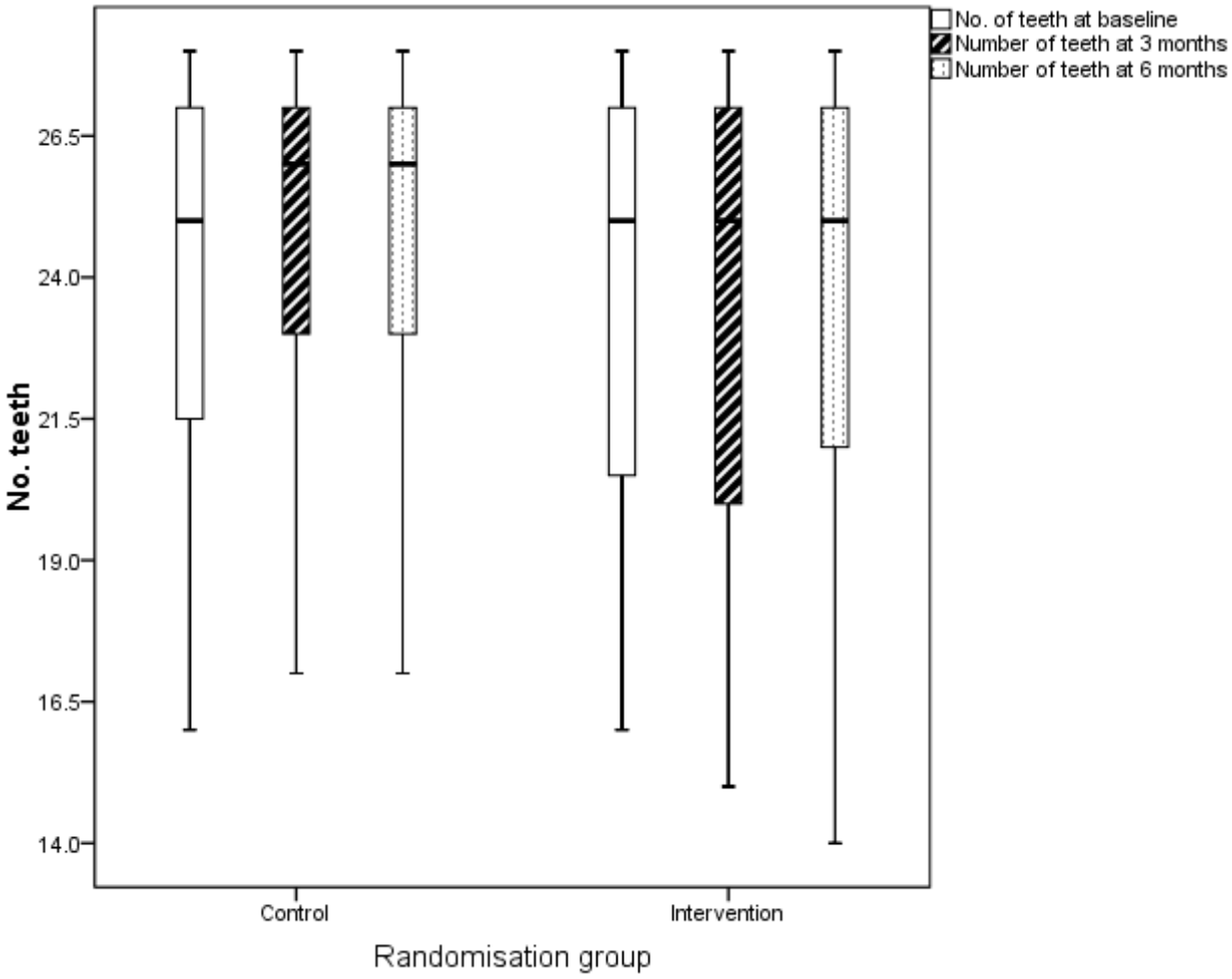

Figure 3.10 Number of teeth present by randomisation group at baseline, 3 months and 6 months.

Boxplot representing five-number summary: minimum value that is no greater than 1.5 times the IQR (lower whisker), 25th percentile (bottom of box), median (dark line in middle), 75th percentile (top of box) and maximum value that is no greater than 1.5 times IQR (upper whisker). Mild outliers (open circles) are values between 1.5 and 3 times the IQR. Extreme outliers (asterisks) are values more than 3 times the IQR.

Mean pocket probing depth

The mean PPD was similar for both groups at baseline, 4.1 mm and 3.9 mm for the control and intervention group respectively. The mean PPD of both groups decreased over the six months of the study, denoting an improvement in periodontal health. The control group reduced by 0.7 mm, whilst the intervention group reduced by 0.8 mm, over the 6 month duration of the study. Figure 3.11 presents the mean PPD by randomisation group at three time points.

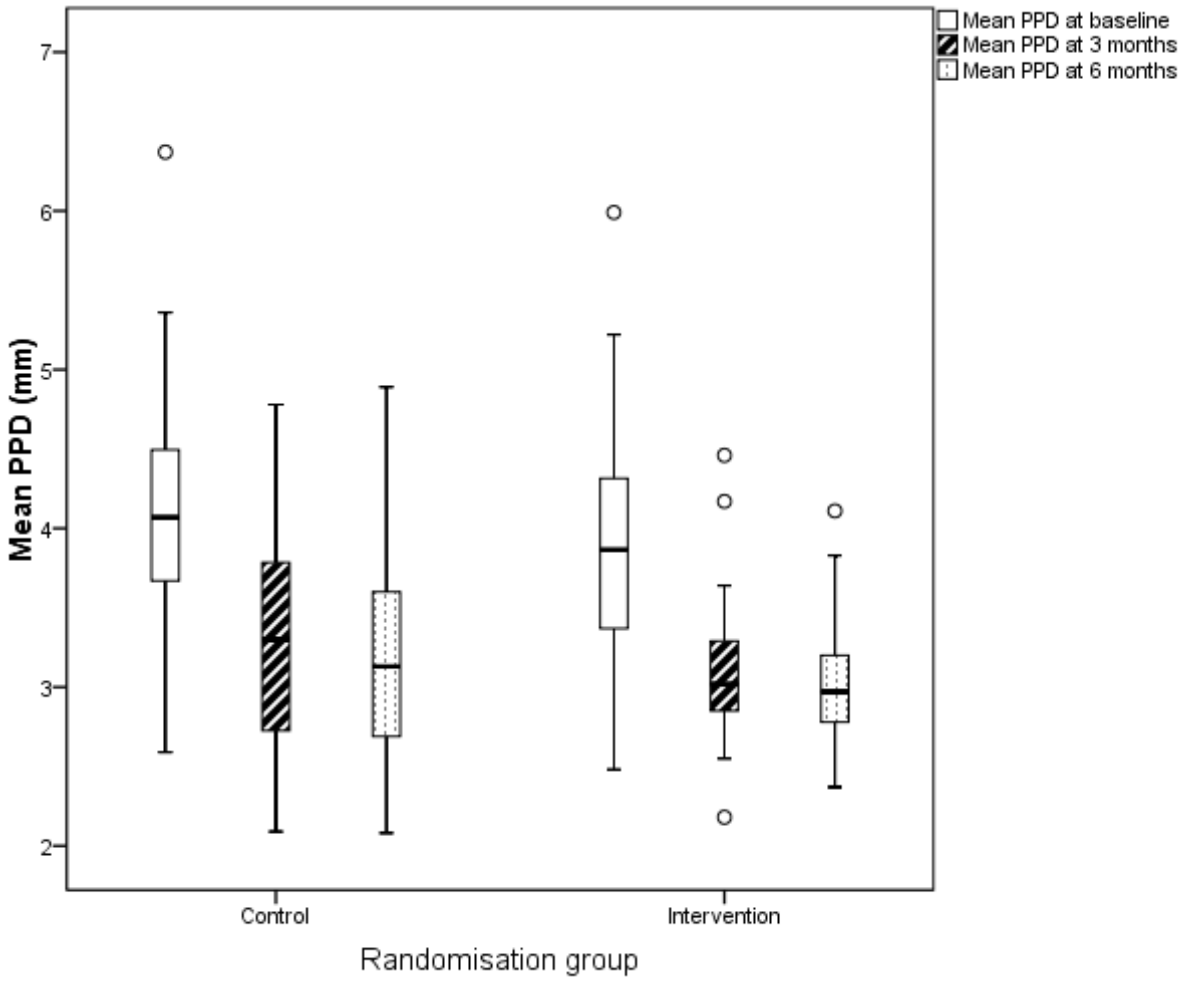

Figure 3.11 Mean PPD (mm) by randomisation group at baseline, 3 months and 6 months.

Boxplot representing five-number summary: minimum value that is no greater than 1.5 times the IQR (lower whisker), 25th percentile (bottom of box), median (dark line in middle), 75th percentile (top of box) and maximum value that is no greater than 1.5 times IQR (upper whisker). Mild outliers (open circles) are values between 1.5 and 3 times the IQR. Extreme outliers (asterisks) are values more than 3 times the IQR.

Percentage of sites with a PPD ≥5 mm

The percentage of sites with a PPD ≥5 mm, an indication of more severe disease, reduced for both groups over the duration of the study. Both groups had approximately 40% of sites in this category at baseline, indicating the severe nature of their periodontal disease. The control and intervention groups demonstrated an absolute reduction in this measure over the study of 19% and 22%, respectively. Figure 3.12 presents the percentage of sites with a PPD ≥5 mm by randomisation group at three time points.

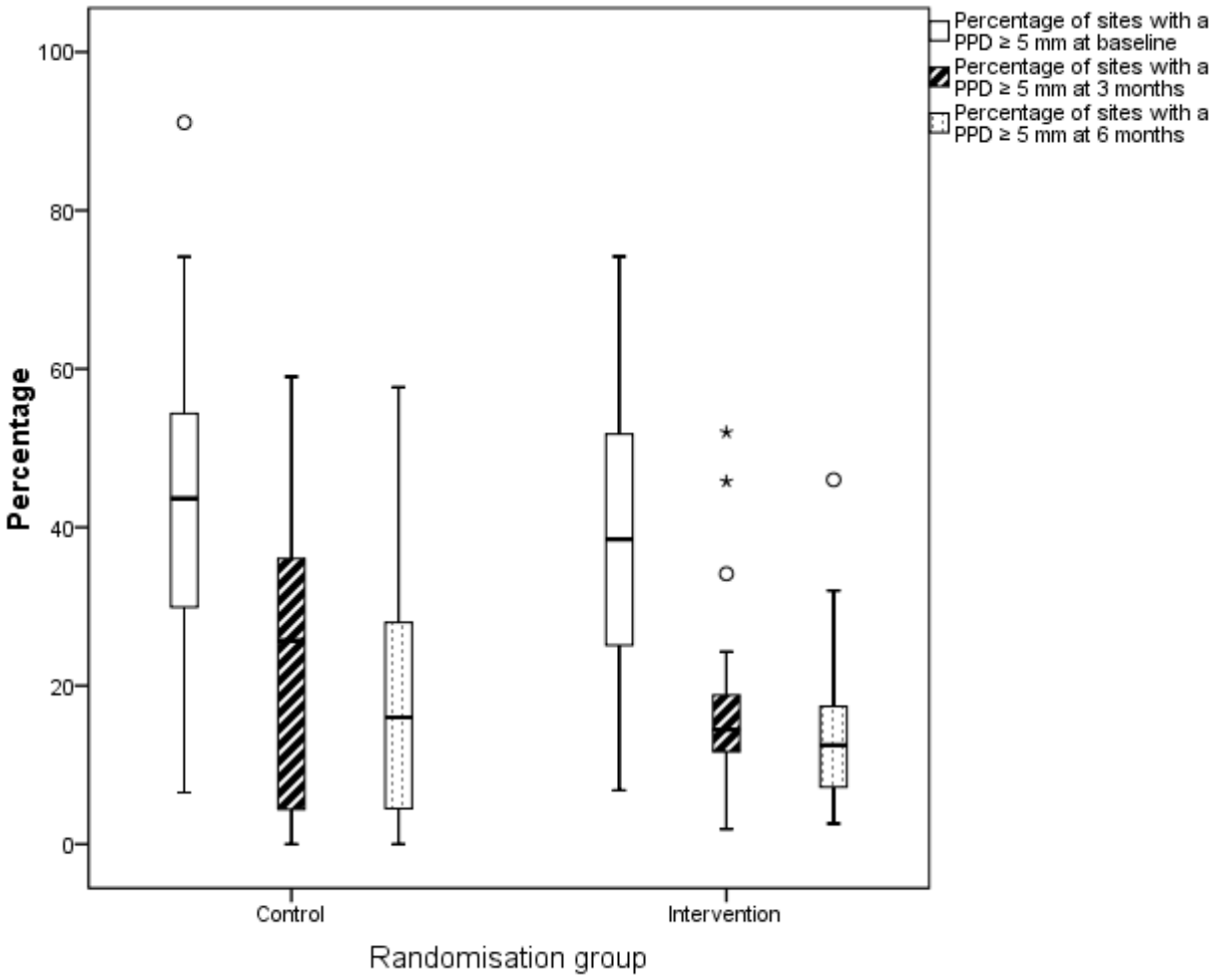

Figure 3.12 Percentage of sites with a PPD ≥5 mm by randomisation groups at baseline, 3 months and 6 months.

Boxplot representing five-number summary: minimum value that is no greater than 1.5 times the IQR (lower whisker), 25th percentile (bottom of box), median (dark line in middle), 75th percentile (top of box) and maximum value that is no greater than 1.5 times IQR (upper whisker). Mild outliers (open circles) are values between 1.5 and 3 times the IQR. Extreme outliers (asterisks) are values more than 3 times the IQR.

Percentage of sites with a PPD >6 mm

The percentage of sites with a PPD >6 mm reduced for both groups over the duration of the study. Both groups had approximately 10% of sites in this category at baseline. The control group reduced by a mean of 5% while the intervention group reduced by 6%. Figure 3.13 presents the percentage of sites with a PPD >6 mm by randomisation group at three time points.

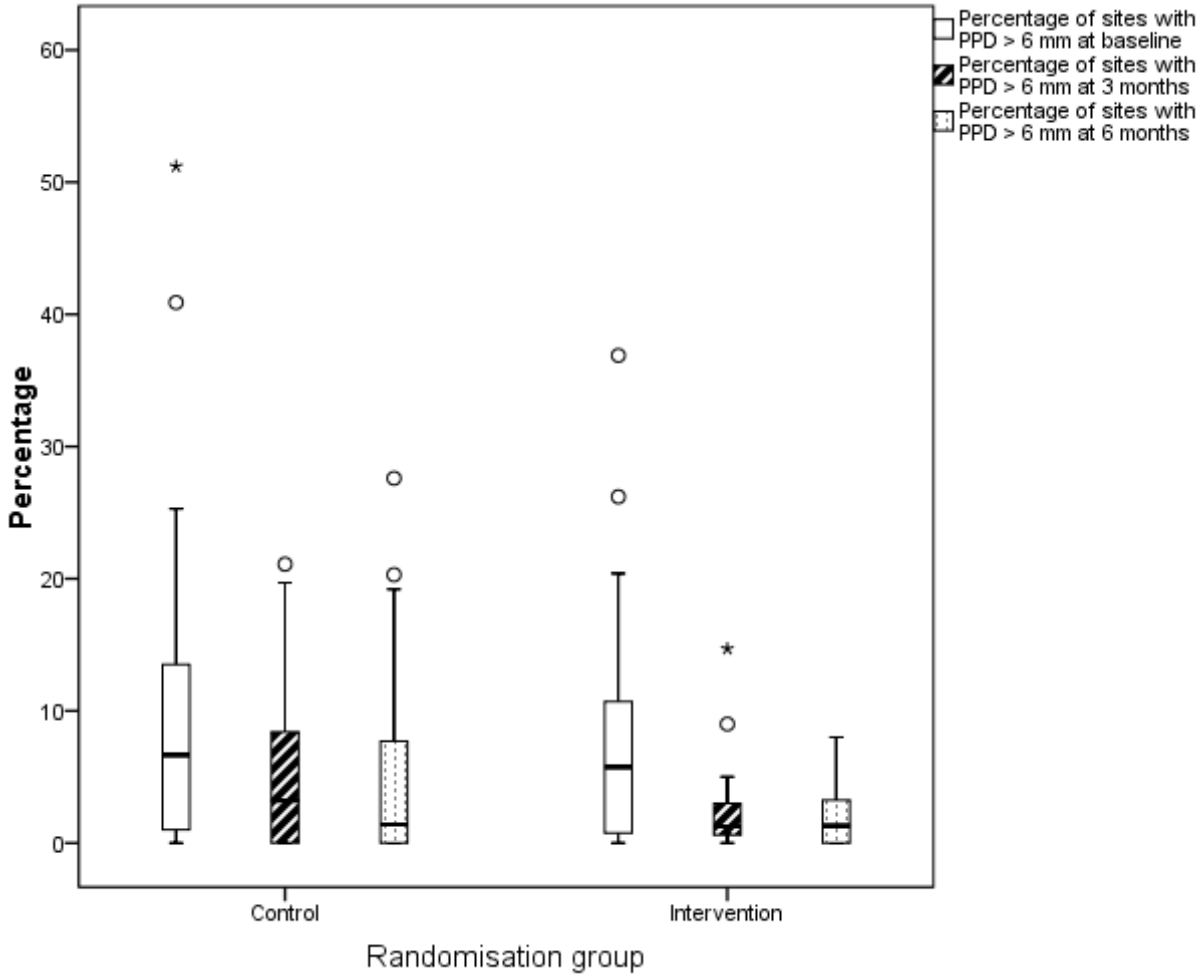

Figure 3.13 Percentage of sites with PPD >6 mm by randomisation group at visit baseline, 3 months and 6 months.

Boxplot representing five-number summary: minimum value that is no greater than 1.5 times the IQR (lower whisker), 25th percentile (bottom of box), median (dark line in middle), 75th percentile (top of box) and maximum value that is no greater than 1.5 times IQR (upper whisker). Mild outliers (open circles) are values between 1.5 and 3 times the IQR. Extreme outliers (asterisks) are values more than 3 times the IQR.

Percentage of sites with a PPD improving by ≥2 mm

The percentage of sites with a PPD improving by ≥2 mm indicates those sites that have had a clinically meaningful improvement (Greenstein, 2003; Addy and Newcombe, 2005). A mean of 25% of sites in the control group improved by ≥2 mm compared to 27% in the intervention group. Figure 3.14 presents the percentage of sites with a PPD improving by ≥2 mm by randomisation group.

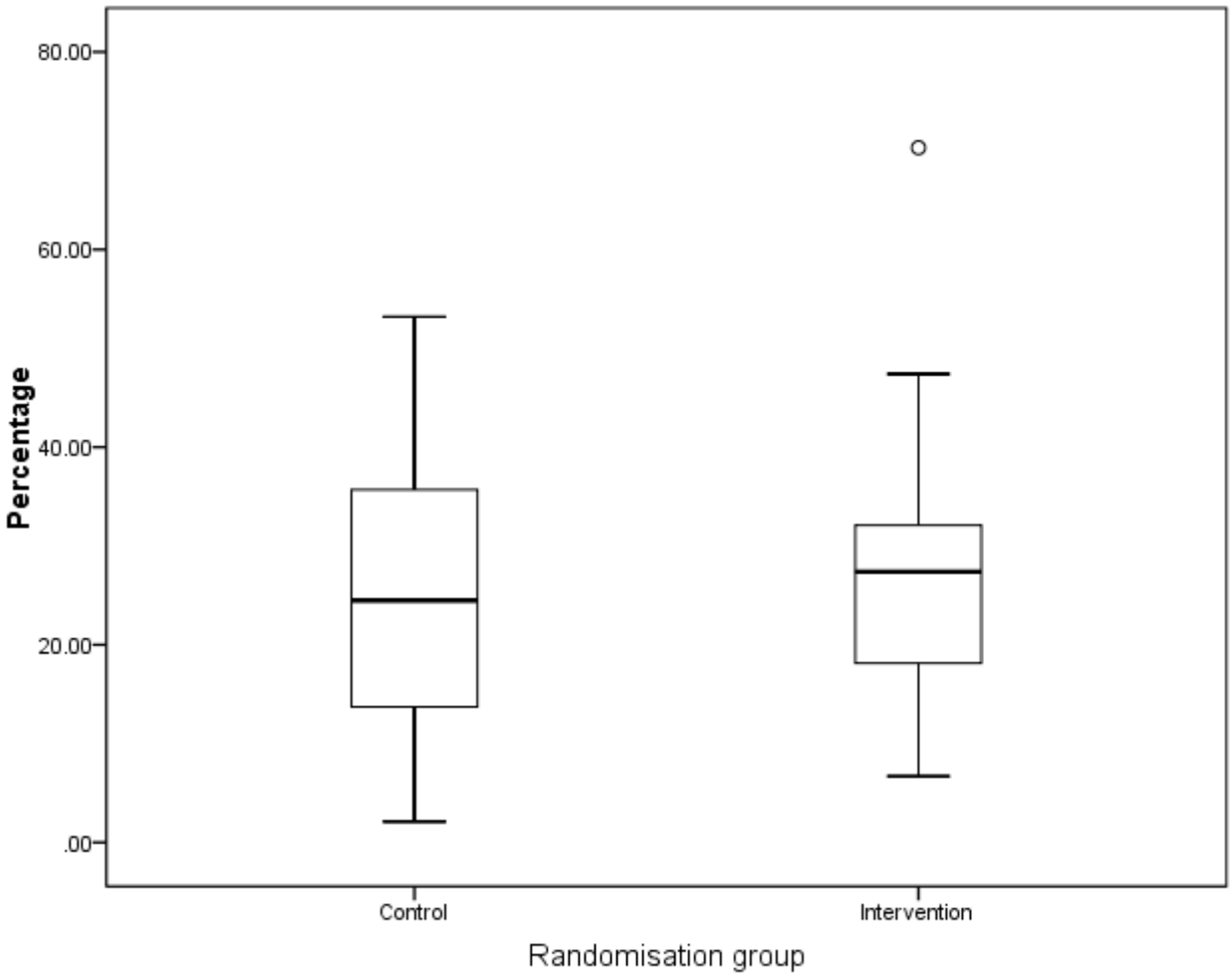

Figure 3.14 Percentage of sites with a PPD improving by ≥2 mm between baseline and 6 months.

Boxplot representing five-number summary: minimum value that is no greater than 1.5 times the IQR (lower whisker), 25th percentile (bottom of box), median (dark line in middle), 75th percentile (top of box) and maximum value that is no greater than 1.5 times IQR (upper whisker). Mild outliers (open circles) are values between 1.5 and 3 times the IQR. Extreme outliers (asterisks) are values more than 3 times the IQR.

Percentage of sites with a PPD improving by ≥3 mm

Similar to the previous measure, the percentage of sites with a PPD improving by ≥3 mm indicates those sites that have had a clinically meaningful improvement. The same percentage of sites (mean = 11%) in both the control and intervention group improved by ≥3 mm between baseline and 6 months. Figure 3.15 presents the percentage of sites with a PPD improving by ≥ 3 mm by randomisation group.

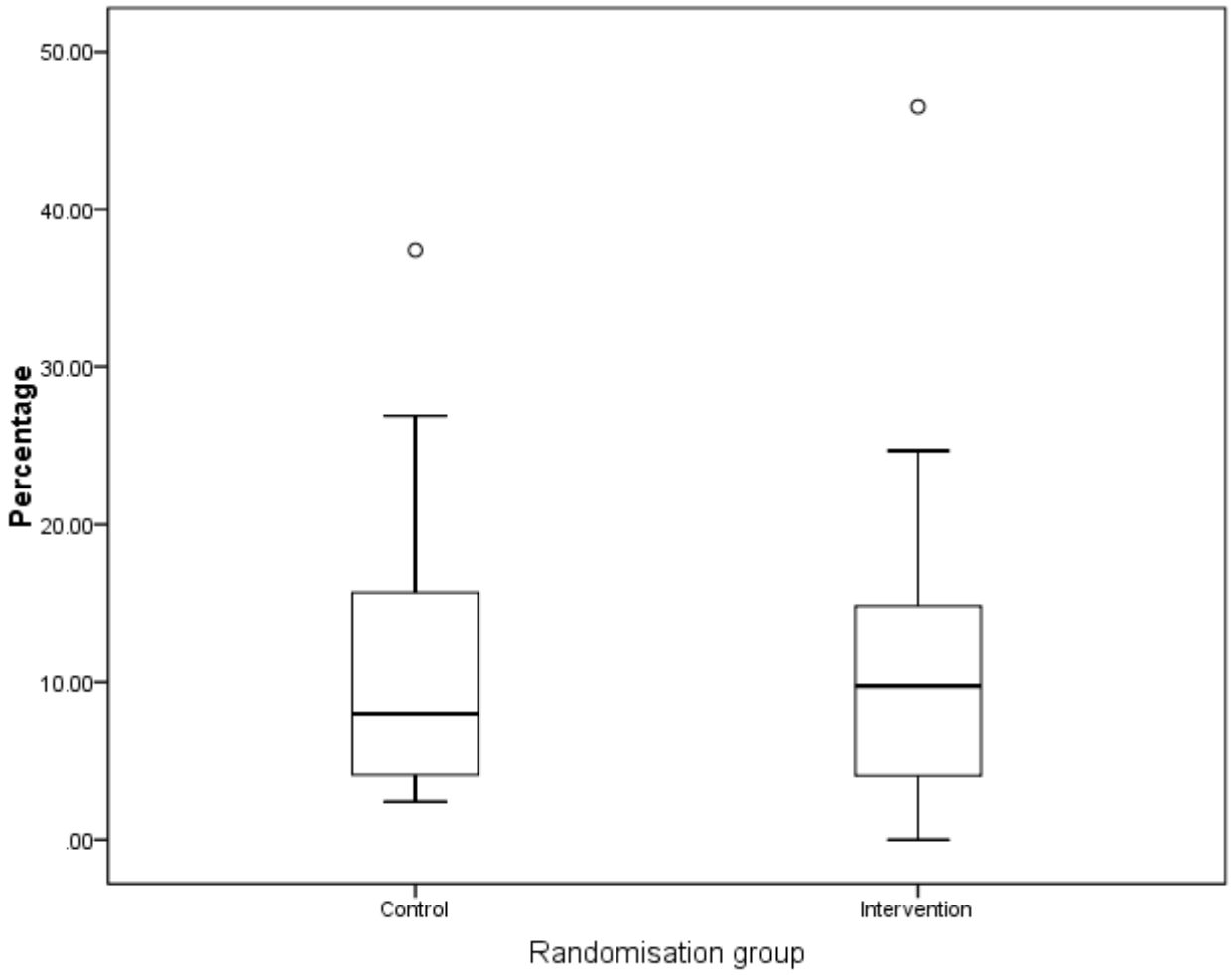

Figure 3.15 Percentage of sites with a PPD improving by ≥3 mm between baseline and 6 months.

Boxplot representing five-number summary: minimum value that is no greater than 1.5 times the IQR (lower whisker), 25th percentile (bottom of box), median (dark line in middle), 75th percentile (top of box) and maximum value that is no greater than 1.5 times IQR (upper whisker). Mild outliers (open circles) are values between 1.5 and 3 times the IQR. Extreme outliers (asterisks) are values more than 3 times the IQR.

Percentage of deep sites improving by ≥2 mm

This measure indicates those deep sites that showed clinically meaningful improvement. Three definitions of deep sites were used: PPD ≥ 4 mm, PPD ≥ 5 mm and PPD ≥ 6 mm. Figure 3.16 presents the percentage of deep sites, using the three definitions that demonstrated clinically meaningful improvement in PPD (≥2 mm).

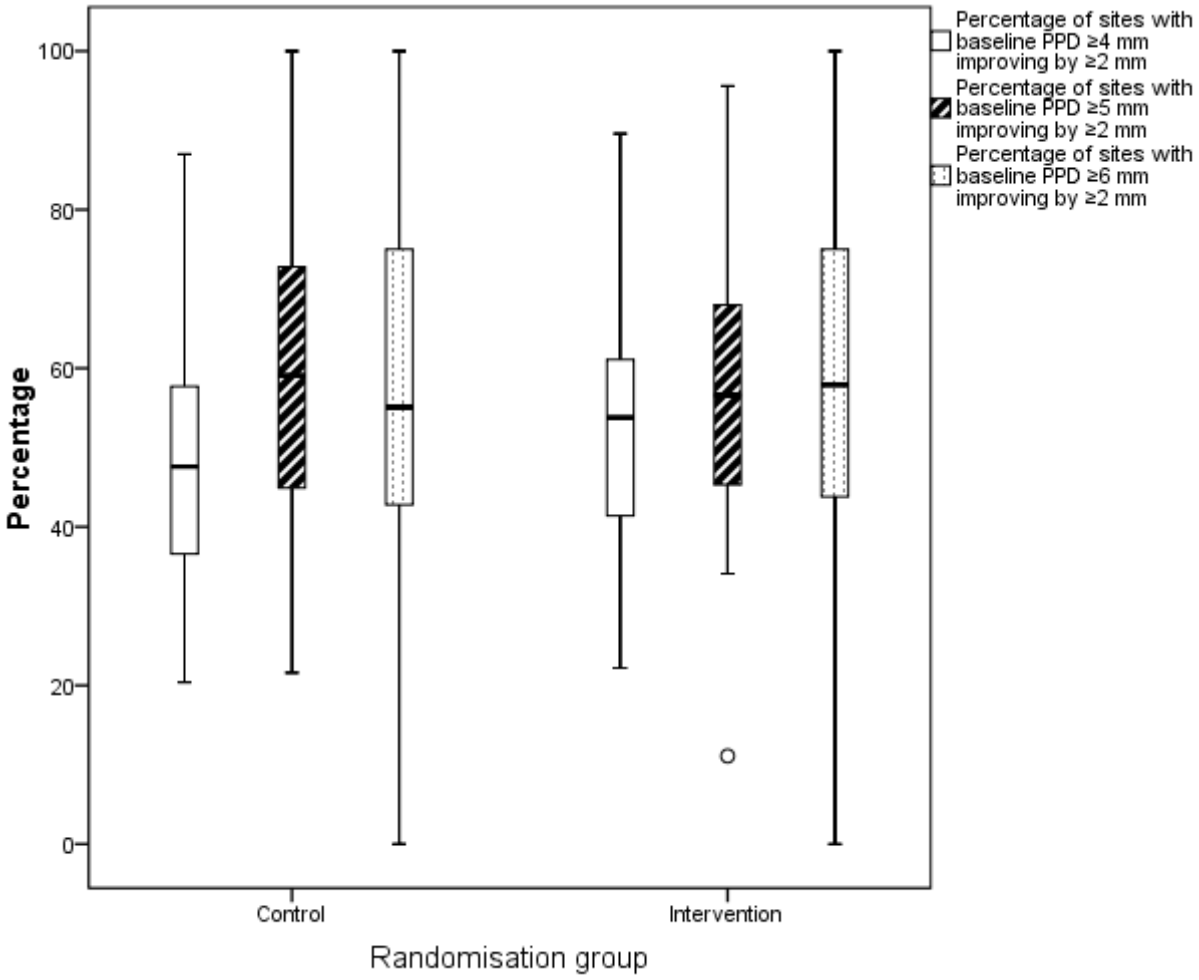

Figure 3.16 Percentage of deep sites improving by ≥2 mm between baseline and 6 months.

Boxplot representing five-number summary: minimum value that is no greater than 1.5 times the IQR (lower whisker), 25th percentile (bottom of box), median (dark line in middle), 75th percentile (top of box) and maximum value that is no greater than 1.5 times IQR (upper whisker). Mild outliers (open circles) are values between 1.5 and 3 times the IQR. Extreme outliers (asterisks) are values more than 3 times the IQR.

Mean modified gingival index

The mean MGI for both groups was similar at baseline (mean of 2.5) and reduced in both groups throughout the study, denoting an improvement in gingival health. The largest reduction was seen during the first three months, with little change thereafter. Over the six month duration of the study the control group had a reduction of 0.5, and the intervention group had a reduction of 0.7. Figure 3.17 presented the MGI by randomisation group at three time points.

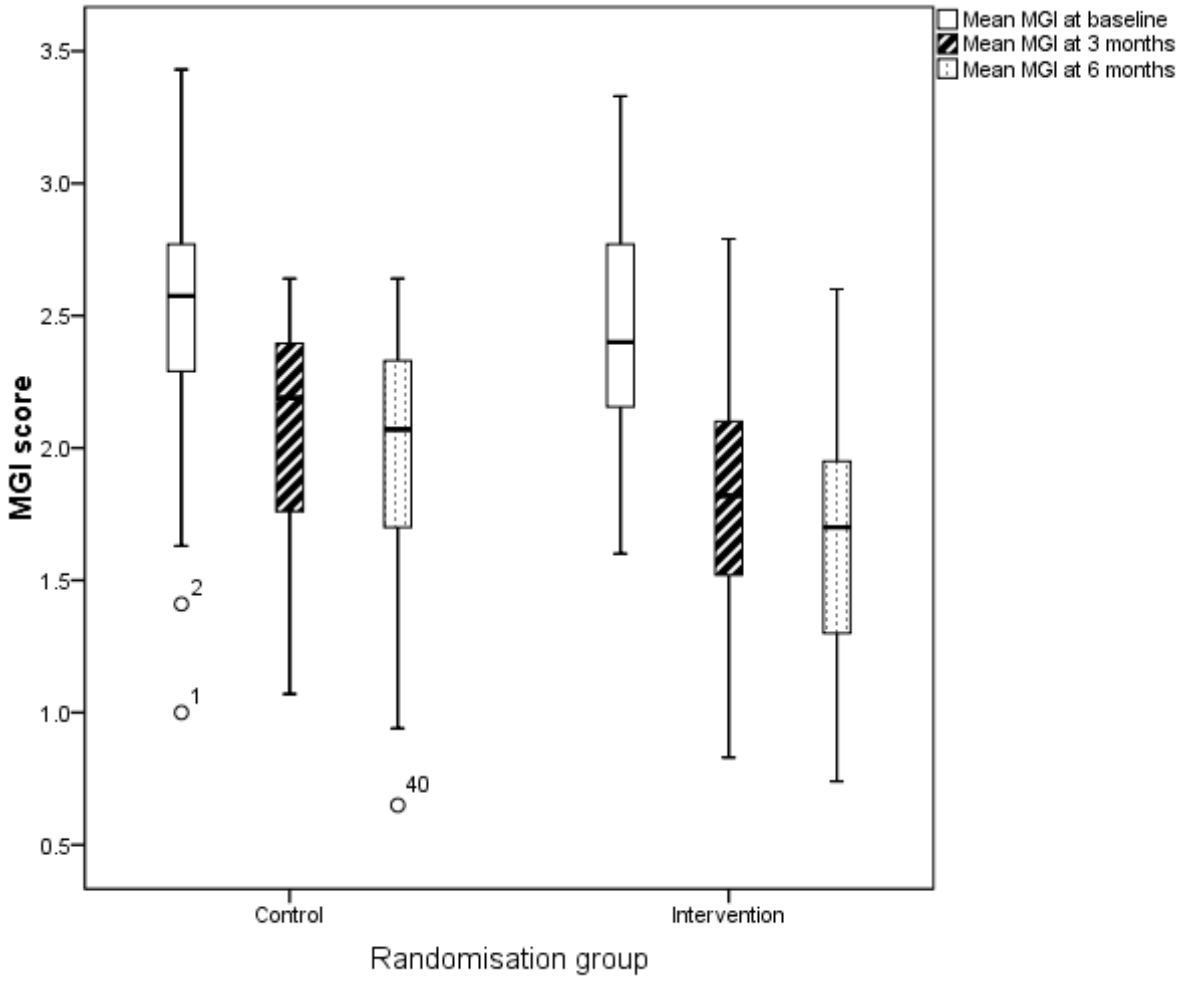

Figure 3.17 Mean MGI by randomisation group at baseline, 3 months and 6 months.

Boxplot representing five-number summary: minimum value that is no greater than 1.5 times the IQR (lower whisker), 25th percentile (bottom of box), median (dark line in middle), 75th percentile (top of box) and maximum value that is no greater than 1.5 times IQR (upper whisker). Mild outliers (open circles) are values between 1.5 and 3 times the IQR. Extreme outliers (asterisks) are values more than 3 times the IQR.

Mean plaque index

The control group had larger baseline scores compared to the intervention group (1.1 versus 0.8). The mean PI reduced in both groups throughout the study. Over the six months of the study the control group had a reduction of 0.6 and the intervention group had a reduction of 0.4. Figure 3.18 presents the mean PI by randomisation group at three time points.

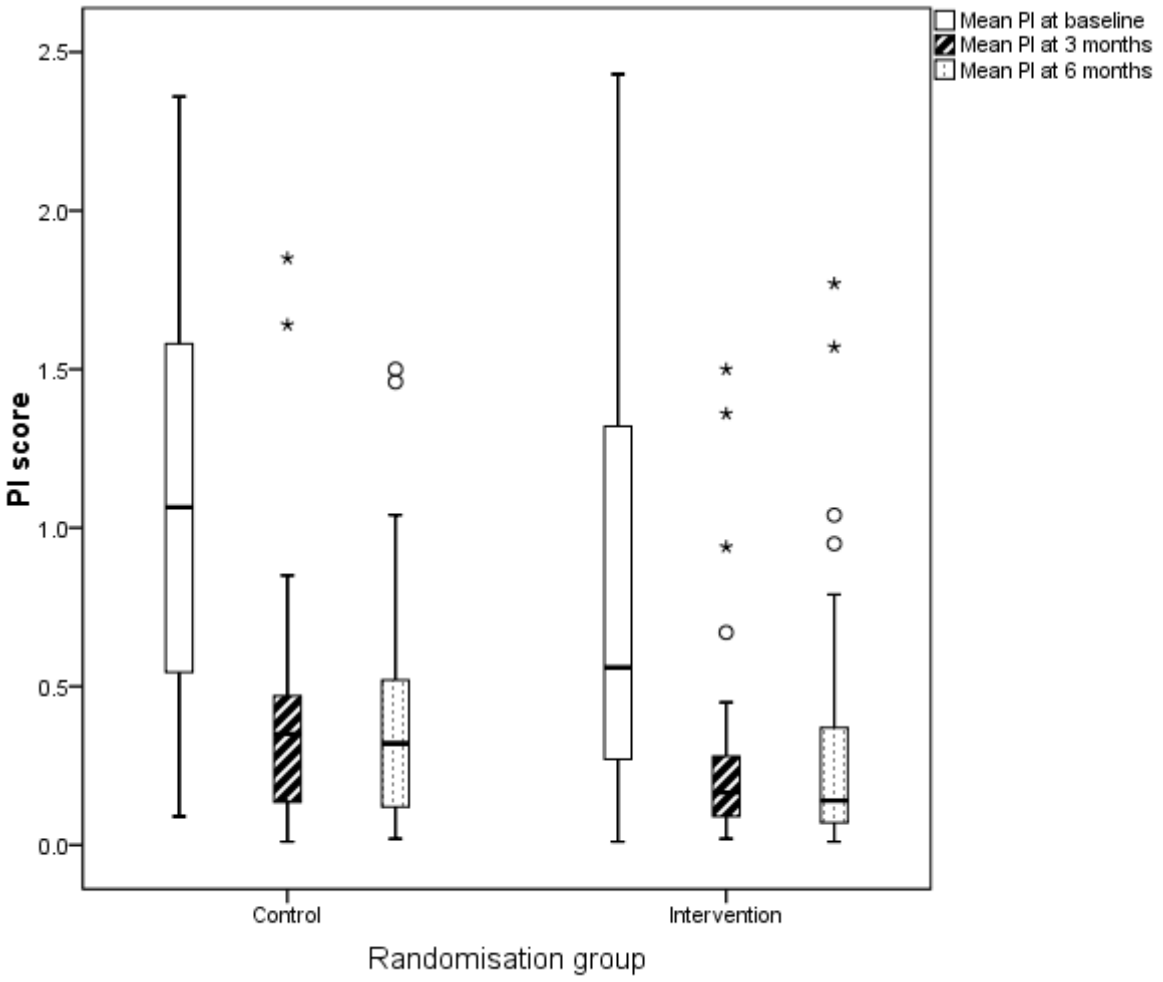

Figure 3.18 Mean PI by randomisation group at baseline, 3 months and 6 months.

Boxplot representing five-number summary: minimum value that is no greater than 1.5 times the IQR (lower whisker), 25th percentile (bottom of box), median (dark line in middle), 75th percentile (top of box) and maximum value that is no greater than 1.5 times IQR (upper whisker). Mild outliers (open circles) are values between 1.5 and 3 times the IQR. Extreme outliers (asterisks) are values more than 3 times the IQR.

Mean clinical attachment level

The mean CAL was similar for the two groups at baseline, 5.2 mm in the control group and 5.1 mm in the intervention group. The mean CAL reduced in both groups throughout the study, denoting improvement in periodontal health. The control and intervention groups had similar mean changes over 6 months with 0.5 mm and 0.6 mm, respectively. Figure 3.19 presents the mean CAL by randomisation group at three time points.

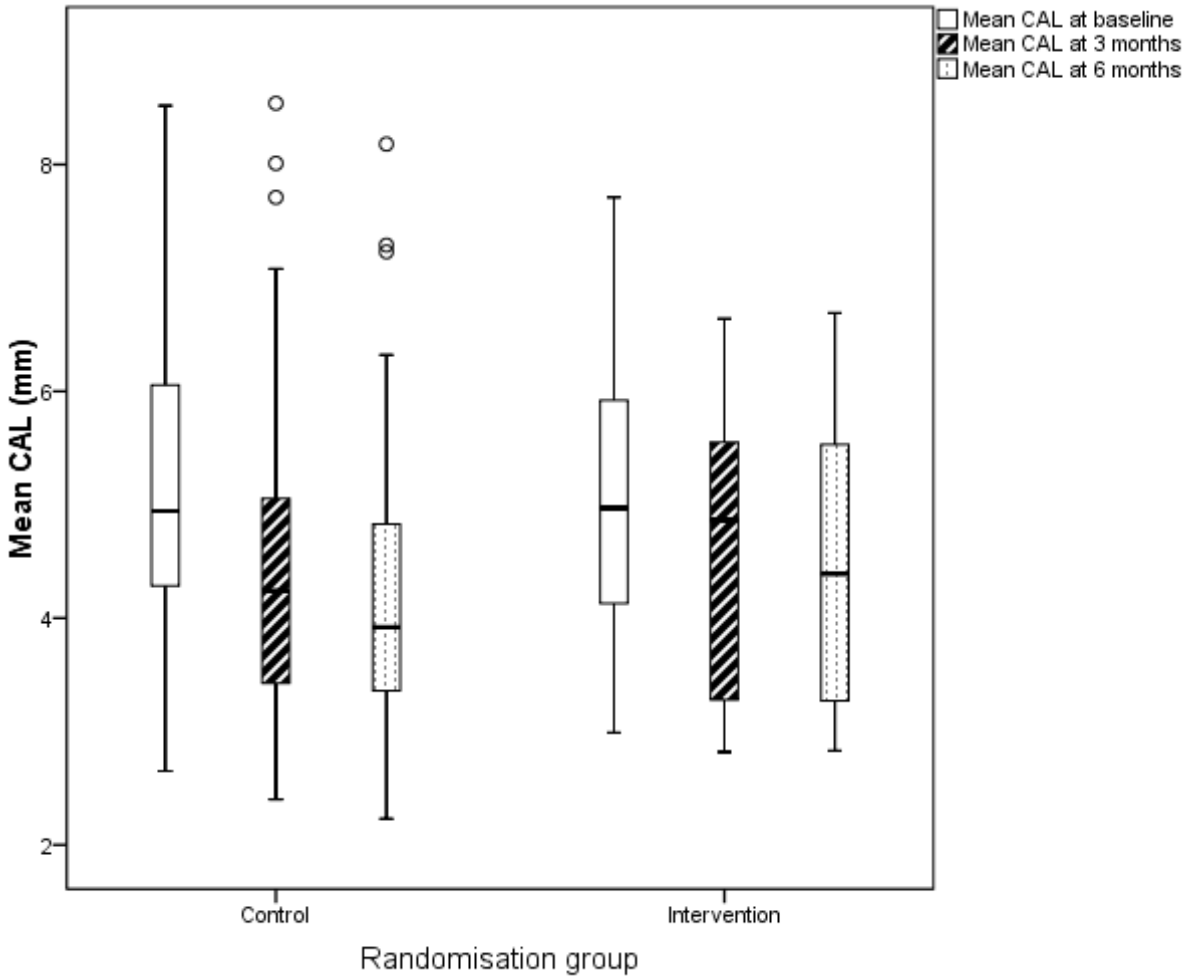

Figure 3.19 Mean CAL by randomisation group at baseline, 3 months and 6 months.

Boxplot representing five-number summary: minimum value that is no greater than 1.5 times the IQR (lower whisker), 25th percentile (bottom of box), median (dark line in middle), 75th percentile (top of box) and maximum value that is no greater than 1.5 times IQR (upper whisker). Mild outliers (open circles) are values between 1.5 and 3 times the IQR. Extreme outliers (asterisks) are values more than 3 times the IQR.

Percentage bleeding on probing

At baseline the control group had a higher percentage BOP compared to the intervention group (24% versus 16%). Over the six months of the study, both groups had absolute reductions in the percentage BOP, by a mean of 11% in the control group and 7% in the intervention group. Figure 3.20 presents the percentage BOP by randomisation group at three time points.

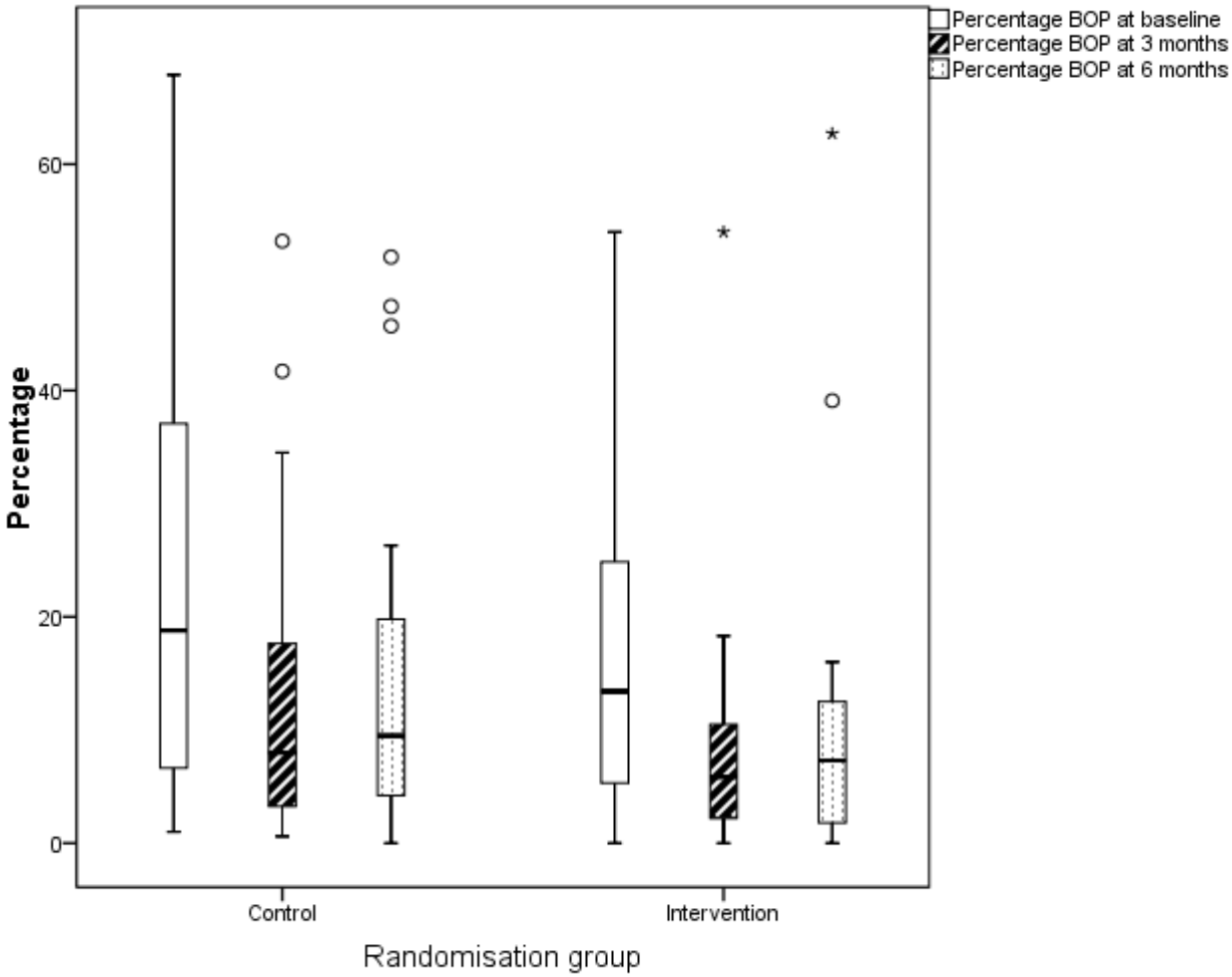

Figure 3.20 Percentage BOP by randomisation group at baseline, 3 months and 6 months.

Boxplot representing five-number summary: minimum value that is no greater than 1.5 times the IQR (lower whisker), 25th percentile (bottom of box), median (dark line in middle), 75th percentile (top of box) and maximum value that is no greater than 1.5 times IQR (upper whisker). Mild outliers (open circles) are values between 1.5 and 3 times the IQR. Extreme outliers (asterisks) are values more than 3 times the IQR.

Clinical oral dryness score

The CODS was similar in both groups at baseline, 4.0 in the control group and 4.1 in the intervention group. The CODS reduced by 1 unit in control group (indicating a reduction in oral dryness) and remained unchanged in the intervention group. Figure 3.21 presents the CODS by randomisation group at three time points

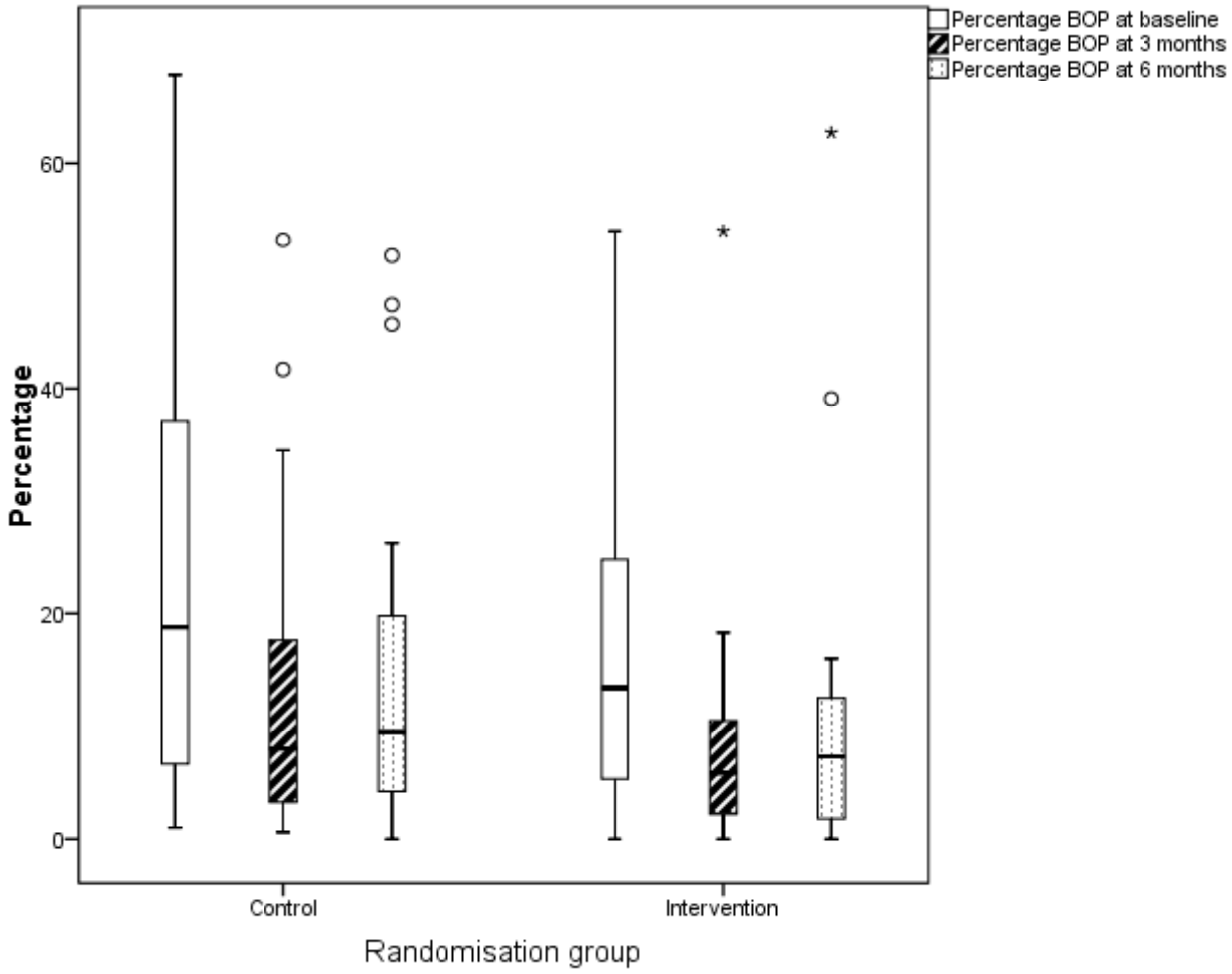

Figure 3.21 CODS by randomisation group at baseline, 3 months and 6 months.

Boxplot representing five-number summary: minimum value that is no greater than 1.5 times the IQR (lower whisker), 25th percentile (bottom of box), median (dark line in middle), 75th percentile (top of box) and maximum value that is no greater than 1.5 times IQR (upper whisker). Mild outliers (open circles) are values between 1.5 and 3 times the IQR. Extreme outliers (asterisks) are values more than 3 times the IQR.

Periodontal epithelial surface area

The PESA was similar in both groups at baseline, although marginally higher in the control group (2134 mm^2 in the control group and 2014 mm^2 in the intervention group). The PESA reduced in both groups during the study, denoting improvement in periodontal health. The control group had a 469 mm^2 PESA reduction and the intervention group had a 569 mm^2 PESA reduction. Figure 3.22 presents the PESA by randomisation group at three time points.

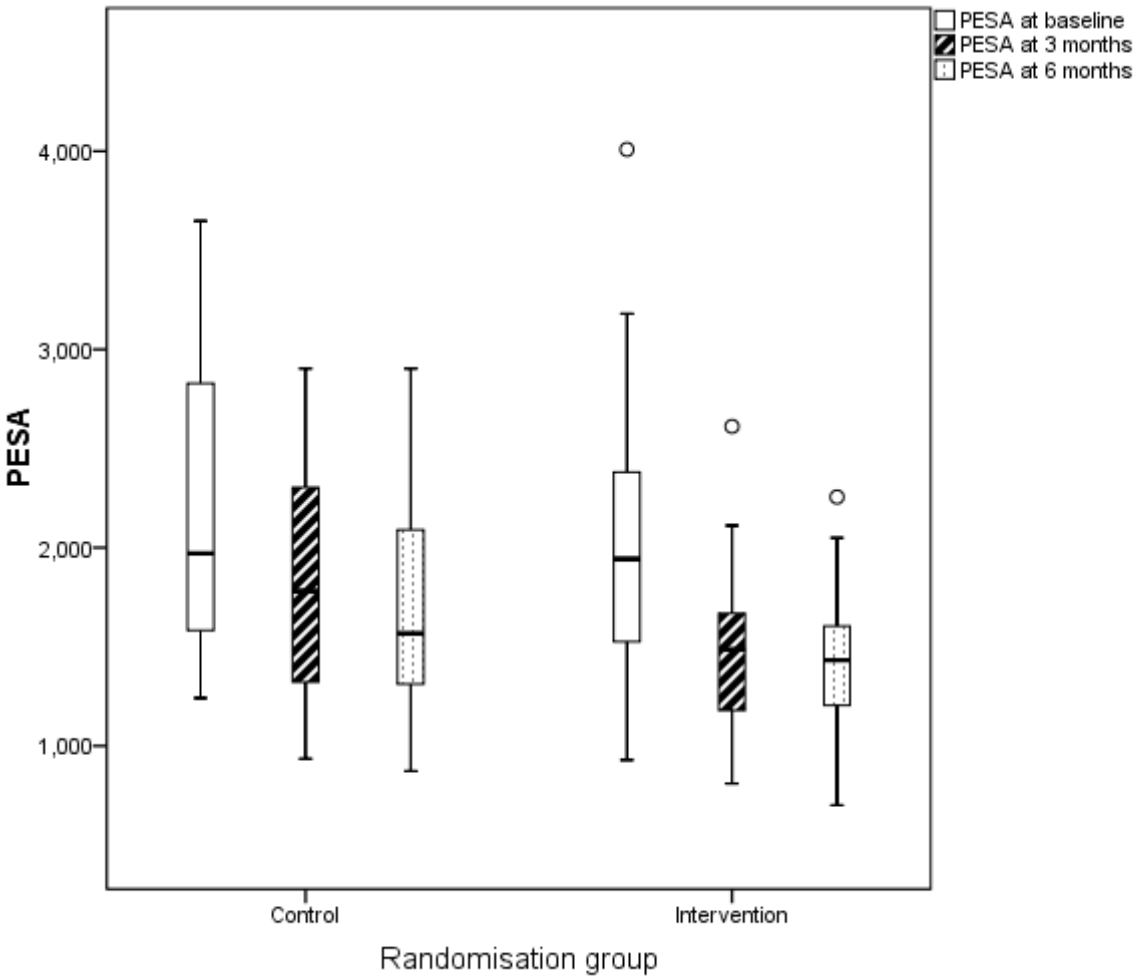

Figure 3.22 PESA by randomisation group at baseline, 3 months and 6 months.

Boxplot representing five-number summary: minimum value that is no greater than 1.5 times the IQR (lower whisker), 25th percentile (bottom of box), median (dark line in middle), 75th percentile (top of box) and maximum value that is no greater than 1.5 times IQR (upper whisker). Mild outliers (open circles) are values between 1.5 and 3 times the IQR. Extreme outliers (asterisks) are values more than 3 times the IQR.

Periodontal inflammed surface area

The PISA was higher in the control group at baseline (635 mm^2 versus 387 mm^2). The PISA reduced in both groups during the study, denoting an improvement in periodontal health. The control group had a 366 mm^2 reduction and the intervention group had a 214 mm^2 reduction. The percentage reductions were similar for both groups (58% versus 55%). Figure 3.23 presents the PISA by randomisation group at three time points.

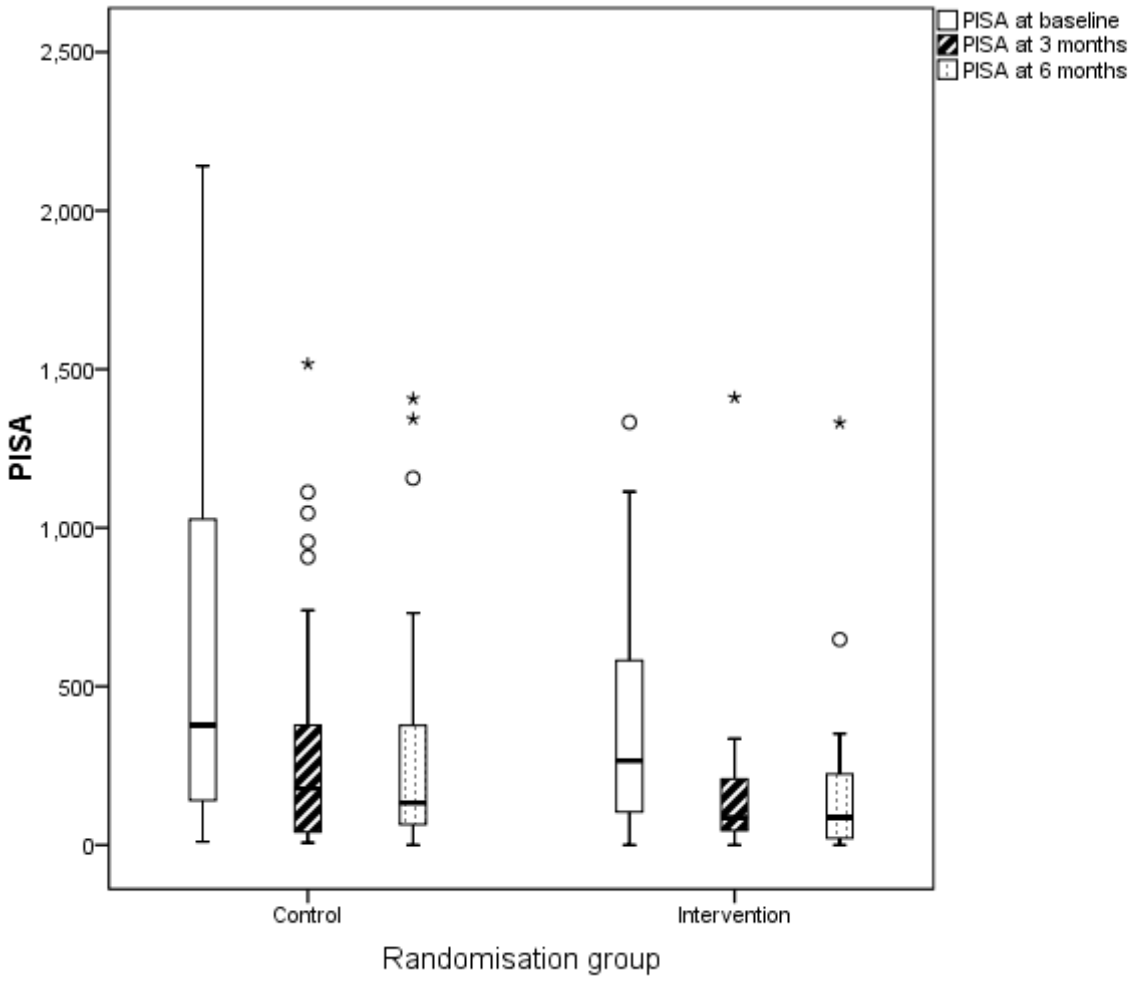

Figure 3.23 PISA by randomisation group at baseline, 3 months and 6 months.

Boxplot representing five-number summary: minimum value that is no greater than 1.5 times the IQR (lower whisker), 25th percentile (bottom of box), median (dark line in middle), 75th percentile (top of box) and maximum value that is no greater than 1.5 times IQR (upper whisker). Mild outliers (open circles) are values between 1.5 and 3 times the IQR. Extreme outliers (asterisks) are values more than 3 times the IQR.

OHQoL-UK

The OHQoL-UK scores were similar for both groups at baseline, 43 in the control group and 44 in the intervention group. This is comparable to a previous study, which reported a mean score of 47 for patients with periodontitis and 53 for periodontally health patients (Durham *et al.*, 2013). The slightly lower scores in the current study, denoting poorer oral health related quality of life, is likely to reflect the more severe disease observed in our sample (e.g. the mean number of sites with PPD ≥5 mm was 33 [Durham *et al.* (2013)] and 57 [current study]). The OHQoL-UK increased in both groups during the study (mean of 9 units in both groups), denoting an improvement in oral health related quality of life. Figure 3.24 presents the OHQoL-UK by randomisation group at two time points.

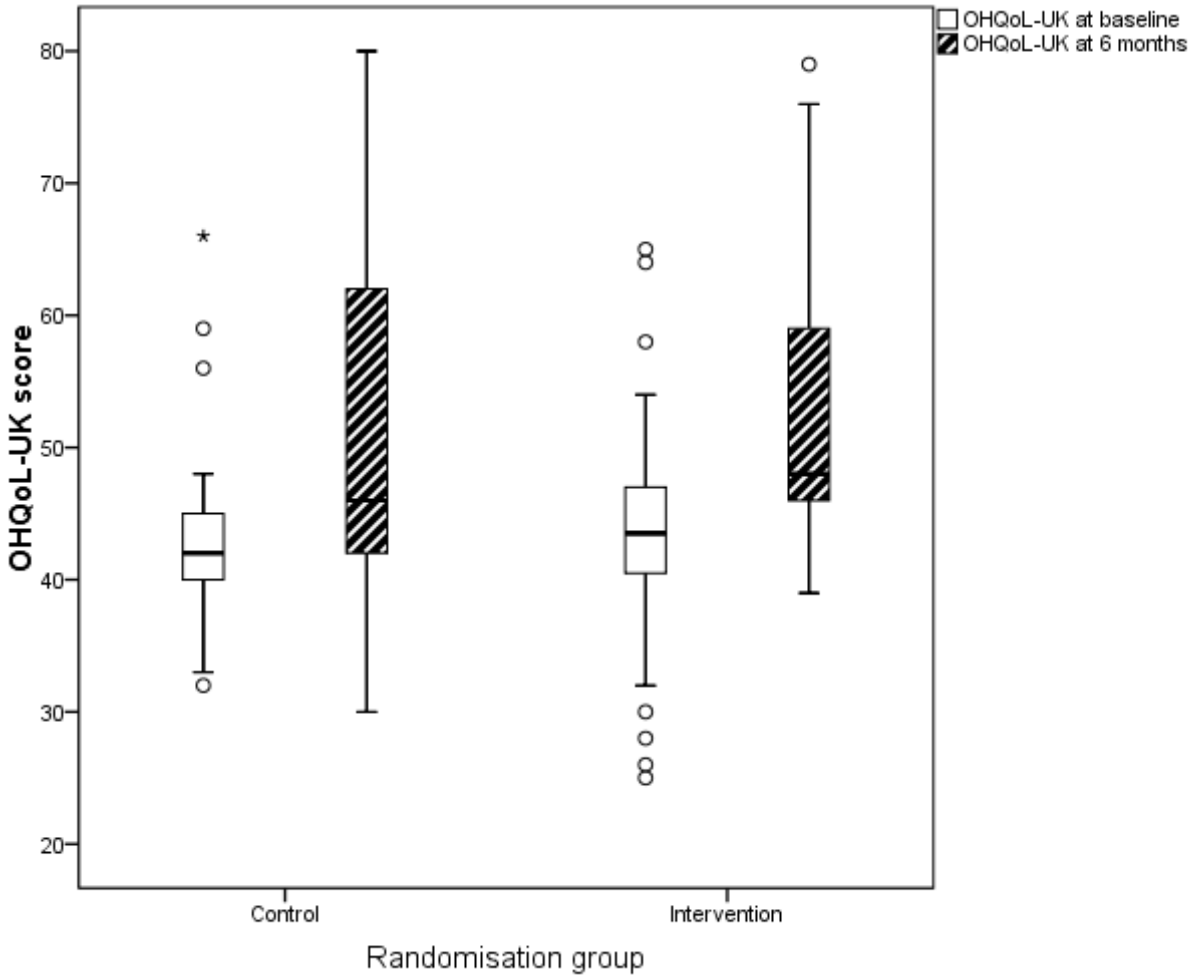

Figure 3.24 OHQoL-UK by randomisation group at baseline and 6 months.

Boxplot representing five-number summary: minimum value that is no greater than 1.5 times the IQR (lower whisker), 25th percentile (bottom of box), median (dark line in middle), 75th percentile (top of box) and maximum value that is no greater than 1.5 times IQR (upper whisker). Mild outliers (open circles) are values between 1.5 and 3 times the IQR. Extreme outliers (asterisks) are values more than 3 times the IQR.

3.5.13 *Comparing novel and traditional periodontal outcome measures*

This study collected a range of traditional periodontal outcome measures such as PPD, CAL, BOP, PI, and MGI. We also calculated the novel outcome measures PESA and PISA. One of the objectives of the pilot RCT was to compare the traditional and novel outcome measures. Figure 3.25 and Figure 3.26 present scatter plots of the novel outcome measures against the key traditional outcome measures. The scatter plots suggest good correlation. This is not surprising since PESA and PISA are derived from PPDs, gingival recession and BOP.

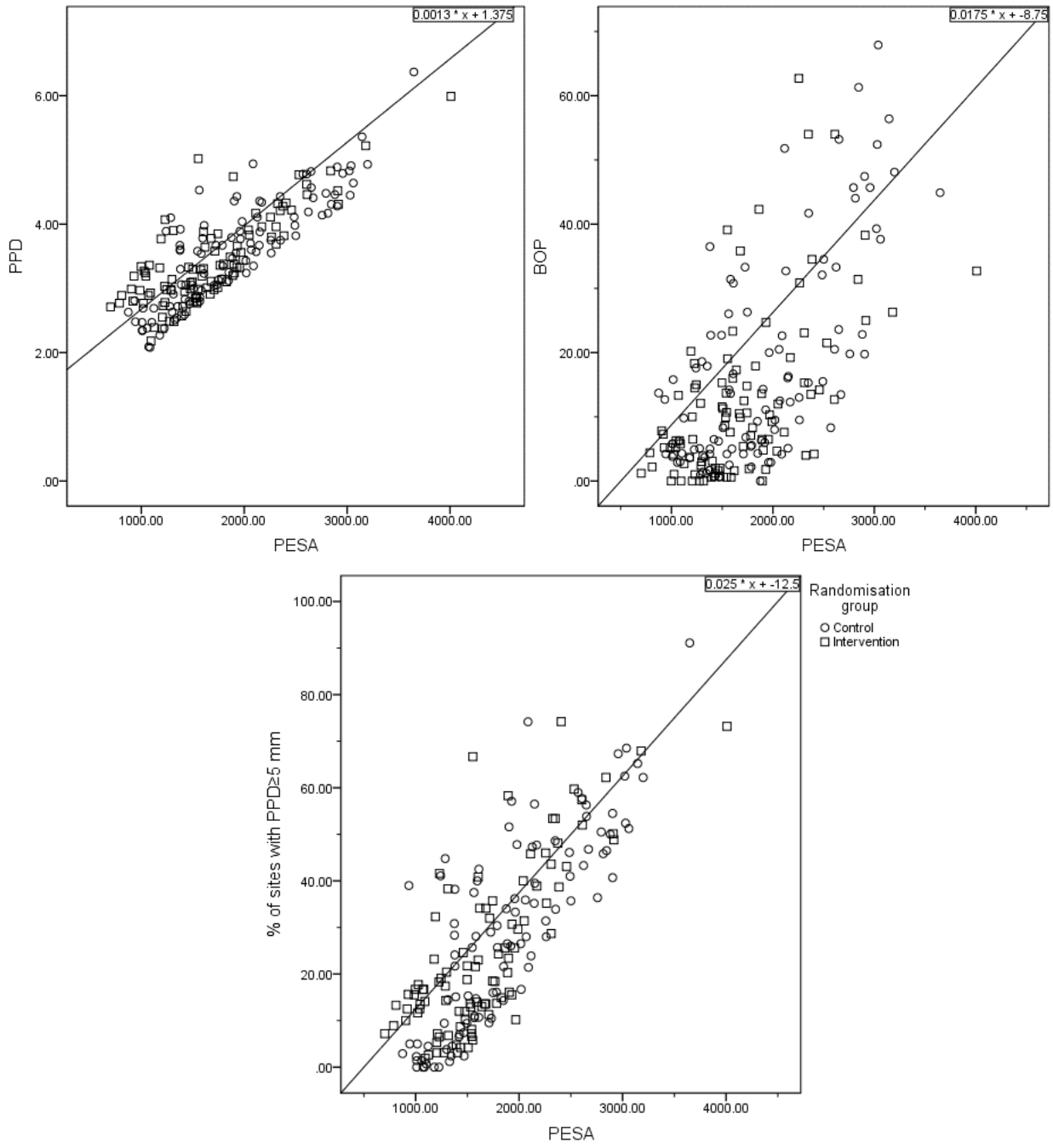

Figure 3.25 Comparison of PESA with PPD, BOP and % of sites with a PPD ≥5 mm.

Data points combined from baseline, 3-month, 6-month visits (n=199).

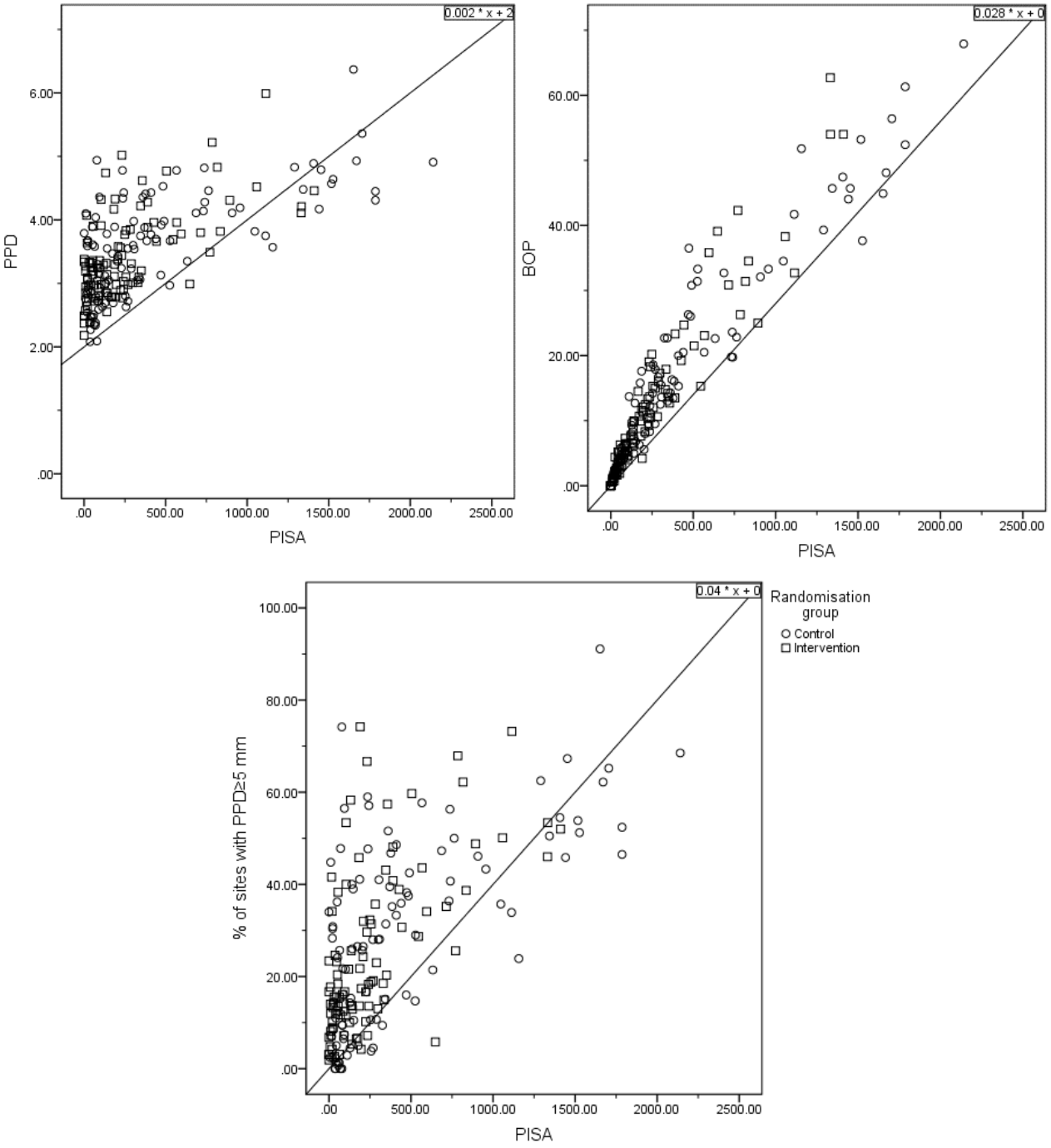

Figure 3.26 Comparison of PISA with PPD, BOP and % of sites with a PPD ≥5 mm.

Data points combined from baseline, 3-month, 6-month visits (n=199).

3.5.14 *Smoking outcome measures*

Outcome	Control Group, n= 40								Intervention Group, n= 40							
Min Median (LQ-UQ) Mean (SD) Max 95% CI *Unless otherwise detailed*	**Baseline (all)**	**Baseline for those reaching 4-week visit**	**Baseline for those reaching 3-month visit**	**Baseline for those reaching 6-month visit**	**Quit date**	**4 weeks**	**3 months**	**6 months**	**Baseline**	**Baseline for those reaching 4-week visit**	**Baseline for those reaching 3-month visit**	**Baseline for those reaching 6-month visit**	**Quit date**	**4 weeks**	**3 months**	**6 months**
FTND	1	1	1	1	0	0	0	0	1	1	1	1	0	0	0	0
	5 (3-7)	5 (3-7)	5(3-6)	5 (3-6)	4 (3-5)	3 (1-4)	3 (1-4)	3 (1-4)	5 (4-6)	5 (4-6)	5 (4-6)	5 (4-5)	3 (0-5)	3 (0-4)	3 (0-4)	3 (0-4)
	5 (2.4)	5 (2.4)	5 (2.4)	5 (2.5)	4 (2.4)	3 (2.1)	3 (2.3)	3 (2.4)	5 (1.8)	5 (1.8)	5 (1.8)	5 (1.6)	3 (2.2)	2 (2.2)	2 (1.8)	3 (2.1)
	9	9	9	9	9	8	8	8	9	9	9	8	7	6	6	7
	4-6	4-6	4-6	4-6	3-5	2-4	2-4	2-4	4-6	4-6	4-6	4-5	3-5	2-3	2-3	2-4
MPSS	14	14	14	14	12	11	10	10	13	14	13	13	12	10	10	10
	21 (18-27)	20 (17-27)	20 (17-27)	21 (18-27)	21 (18-26)	19 (15-23)	20 (14-22)	17 (14-27)	22 (19-26)	21 (19-26)	20 (19-26)	20 (19-26)	21 (17-24)	20 (17-24)	19 (15-21)	17 (15-21)
	23 (7.0)	22 (7.2)	23 (7.3)	23 (7.5)	23 (6.9)	20 (6.3)	19 (5.2)	20 (7.2)	23 (5.9)	22 (4.8)	22 (5.0)	22 (4.9)	21 (5.5)	20 (5.0)	19 (4.8)	19 (7.7)
	44	44	44	44	41	36	29	36	40	34	34	34	33	29	29	52
	21-25	20-25	20-25	20-26	20-25	18-22	17-21	17-23	21-25	20-24	20-24	20-24	20-23	18-22	17-21	16-22
MPSS (M)	7	7	7	7	7	7	7	7	7	7	7	8	7	7	7	7
	12 (9-15)	11 (9-15)	11 (9-15)	12 (10-15)	13 (10-17)	10 (9-15)	11 (8-13)	11 (9-17)	12 (10-16)	12 (10-15)	12 (10-15)	11 (10-15)	13 (9-15)	13 (10-15)	11 (9-15)	10 (9-13)
	13 (4.8)	13 (4.9)	13 (4.8)	13 (4.9)	13 (4.9)	12 (5.0)	11 (3.7)	13 (5.3)	13 (5.0)	13 (3.9)	13 (3.9)	12 (3.9)	13 (4.2)	13 (4.0)	12 (3.6)	12 (5.2)
	25	25	25	25	25	23	20	23	26	22	22	22	23	22	20	35
	11-14	11-15	11-15	11-15	12-15	11-14	10-13	11-15	12-15	11-14	11-14	11-14	11-14	11-14	10-13	10-14
MPSS (C)	2	2	3	3	0	0	0	0	2	2	2	2	0	0	0	0
	5 (4-7)	5 (4-6)	5 (4-6)	5 (6-7)	5 (4-6)	4 (3-5)	4 (3-5)	3 (2-6)	5 (4-6)	5 (4-6)	5 (4-6)	5 (4-6)	4 (3-5)	4 (2-4)	4 (2-4)	4 (2-5)
	5 (1.7)	5 (1.7)	5 (1.6)	5 (1.6)	5 (2.1)	4 (1.6)	4 (2.1)	4 (2.4)	5 (1.7)	5 (1.5)	5 (1.5)	5 (1.3)	4 (2.0)	3 (1.9)	3 (1.8)	3 (2.3)
	9	9	9	9	10	7	9	10	10	10	9	8	10	10	7	10
	5-6	5-6	5-6	5-6	4-5	3-4	3-5	3-4	5-6	4-5	4-5	4-5	4-5	3-4	3-4	2-4
MPSS (P)	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3	3
	4 (3-5)	4 (3-5)	4 (3-5)	4 (3-5)	4 (3-4)	3 (3-4)	3 (3-4)	3 (3-4)	4 (3-6)	4 (3-6)	4 (3-6)	4 (3-6)	4 (3-5)	4 (3-4)	4 (3-5)	4 (3-5)
	5 (2.1)	5 (2.1)	4 (2.2)	4 (2.3)	4 (2.1)	4 (1.4)	4 (1.2)	4 (1.2)	5 (1.9)	5 (1.7)	5 (1.7)	5 (1.8)	5 (1.4)	4 (1.1)	4 (1.7)	4 (1.2)
	13	13	13	13	14	9	8	8	10	9	9	9	8	8	10	7
	4-5	4-5	4-5	4-5	4-5	3-4	3-4	3-4	4-5	4-5	4-5	4-5	4-5	3-4	4-5	4-5

Outcome	Control Group, n= 40									Intervention Group, n= 40						
Min Median (LQ-UQ) Mean (SD) Max 95% CI *Unless otherwise detailed*	**Baseline (all)**	**Baseline for those reaching 4-week visit**	**Baseline for those reaching 3-month visit**	**Baseline for those reaching 6-month visit**	**Quit date**	**4 weeks**	**3 months**	**6 months**	**Baseline**	**Baseline for those reaching 4-week visit**	**Baseline for those reaching 3-month visit**	**Baseline for those reaching 6-month visit**	**Quit date**	**4 weeks**	**3 months**	**6 months**
eCO (ppm)	1 18 (10-26) 18 (10.0) 49 15-21	1 14 (10-25) 17 (10.2) 49 14-21	1 14 (10-25) 17 (10.1) 49 13-21	1 14 (10-25) 17 (10.4) 49 13-21	0 20 (12-27) 20 (12.1) 52 16-24	0 15 (10-25) 17 (12.5) 64 13-21	0 11 (2-17) 11 (8.6) 30 8-14	0 10 (2-21) 11 (9.8) 32 8-15	6 22 (12-32) 23 (12.2) 55 19-27	7 25 (12-33) 23 (12.4) 55 19-28	6 24 (12-33) 23 (13.2) 55 19-28	6 20 (11-31) 22 (12.8) 55 17-27	0 12 (3-20) 15 (14.0) 53 10-19	0 8 (2-19) 12 (12.1) 46 7-16	0 8 (3-16) 10 (9.5) 44 7-14	0 7 (2-17) 10 (8.3) 29 7-13
SC (ng/ml)	0 322 (203-382) 303 (128.3) 541 261-346	0 297(182-366) 284 (124.0) 522 240-328	0 292 (182-367) 281 (127.6) 522 233-330	0 287 (163-371) 277 (131.5) 522 225-329	0 314 (185-385) 296 (136.4) 552 251-341	0 297 (167-372) 282 (141.1) 522 233-330	-	0 221 (87-347) 230 (169.1) 560 165-294	133 310 (265-433) 343 (138.1) 754 298-387	161 307 (265-423) 342 (143.0) 754 290-393	133 308 (261-436) 342 (146.5) 754 290-394	133 298 (220-381) 326 (145.5) 754 271-382	6 282 (221-366) 308 (173.5) 850 251-366	3 270 (167-372) 278 (191.5) 984 209-347	-	0 241 (172-352) 264 (164.2) 683 202-327
SA (ng/ml)	0 0.7 (0.2-1.7) 1.1 (1.4) 7.3 0.7-1.6	0 0.6 (0.2-1.2) 0.8 (0.8) 3.0 0.5-1.1	0 0.6 (0.2-1.1) 0.8 (0.8) 3.0 0.5-1.1	0 0.6 (0.2-1.1) 0.8 (0.8) 3.0 0.5-1.1	0 0.7 (0.4-1.3) 1.1 (1.3) 7.5 0.7-1.5	0 0.5 (0.2-1.1) 0.8 (0.8) 3.4 0.5-1.0	-	0 0.4 (0.1-1.1) 1.2 (2.4) 12.6 0.3-2.1	0.1 0.9 (0.5-1.3) 1.2 (1.2) 5.4 0.8-1.5	0.1 0.9 (0.4-1.3) 1.2 (1.3) 5.4 0.7-1.7	0.1 1.1 (0.5-1.4) 1.2 (1.3) 5.4 0.8-1.7	0.1 1.0 (0.4-1.4) 1.2 (1.3) 5.4 0.7-1.7	0 0.4 (0.2-1.0) 0.8 (1.6) 10.0 0.3-1.4	0 0.4 (0.1-0.8) 0.8 (2.1) 12.0 0.1-1.6	-	0 0.4 (0.1-1.4) 0.8 (1.0) 4.4 0.4-1.2

Outcome	Control Group, n= 40								Intervention Group, n= 40							
Min Median (LQ-UQ) Mean (SD) Max 95% CI *Unless otherwise detailed*	**Baseline (all)**	**Baseline for those reaching 4-week visit**	**Baseline for those reaching 3-month visit**	**Baseline for those reaching 6-month visit**	**Quit date**	**4 weeks**	**3 months**	**6 months**	**Baseline**	**Baseline for those reaching 4-week visit**	**Baseline for those reaching 3-month visit**	**Baseline for those reaching 6-month visit**	**Quit date**	**4 weeks**	**3 months**	**6 months**
SA: Proportion of participants with readings below 0.1ng/ml.	7.5% [n=3]	-	-	-	13% [n=5]	15% [n=6]	-	15% [n=6]	0% [n=0]	-	-	-	18% [n=7]	25% [n=10]	-	18% [n=7]
Self-reported daily smoking amount for all participants (cigarettes/ day)	10 15 (11-20) 17 (7.0) 30 15-20	10 15 (10-20) 17 (7.0) 30 15-20	10 15 (10-20) 17 (7.4) 30 14-20	10 15 (10-23) 17 (7.6) 30 15-20	0 11 (5-18) 13 (9.0) 30 10-16	0 10 (4-15) 10 (7.8) 30 8-13	0 9 (3-15) 9.5 (7.8) 30 7-12	0 5 (1-15) 9 (8.1) 25 5-12	10 15 (15-20) 17 (6.4) 40 15-19	10 15 (15-20) 18 (6.4) 40 15-20	10 15 (15-20) 18 (6.7) 40 15-20	10 15 (13-20) 16 (4.4) 25 14-18	0 5 (0-11) 8 (8.6) 30 5-11	0 5 (0-14) 7 (9.1) 30 4-11	0 5 (0-11) 7 (7.1) 25 4-9	0 8 (0-12) 8 (7.2) 25 5-11

Outcome	Control Group, n= 40								Intervention Group, n= 40							
Min Median (LQ-UQ) Mean (SD) Max 95% CI *Unless otherwise detailed*	**Baseline (all)**	**Baseline for those reaching 4-week visit**	**Baseline for those reaching 3-month visit**	**Baseline for those reaching 6-month visit**	**Quit date**	**4 weeks**	**3 months**	**6 months**	**Baseline**	**Baseline for those reaching 4-week visit**	**Baseline for those reaching 3-month visit**	**Baseline for those reaching 6-month visit**	**Quit date**	**4 weeks**	**3 months**	**6 months**
Self-reported daily smoking amount for only those smoking (cigarettes/ day)	10 15 (11-20) 17 (6.9) 30 15-20	10 15 (10-20) 17 (6.9) 30 15-20	10 15 (10-20) 17 (7.4) 30 14-20	10 15 (10-23) 17 (7.6) 30 14-20	1 12 (5-19) 14 (8.7) 30 11-17	2 10 (5-15) 11 (7.4) 30 9-14	1 10 (5-15) 11 (7.5) 30 8-13	1 10 (5-20) 11 (7.7) 25 8-14	10 15 (13-20) 17 (6.4) 40 15-19	10 15 (15-20) 18 (6.4) 40 15-20	10 15 (15-20) 18 (6.7) 40 15-20	10 15 (15-20) 16 (4.4) 25 14-18	1 9 (5-15) 11 (8.4) 30 7-14	2 7 (5-19) 12 (9.1) 30 7-16	1 9 (5-15) 9 (6.7) 25 7-12	2 10 (6-15) 11 (6.1) 25 8-14
Cumulative self-reported burnt tobacco use	Not able to be calculated due to incomplete weekly questionnaires data															
Cumulative self-reported e-cigarette use (No. of days using e-cigarette) of those attending all visits (n=20)	-	-	-	-	-	-	-	-	-	-	-	-	-	-	-	100 198 (181-217) 196 (40.2) 291 177-215

Table 3.36 Smoking outcome measures- continuous.

Outcome	Control Group, n= 40				Intervention Group, n=40			
n % 95% CI	Quit date	4 weeks	3 months	6 months	Quit date	4 weeks	3 months	6 months
Self-reported quitters of burnt tobacco	2 5% 1%-17%	2 5% 1%-17%	3 8% 3%-20%	4 10% 4%-23%	9 23% 12%-38%	11 28% 16%-43%	9 23% 12%-38%	8 20% 11%-35%
eCO verified self-reported quitter	1 3% 0%-13%	1 3% 0%-13%	1 3% 0%-13%	3 8% 3%-20%	9 23% 12%-38%	11 28% 16%-43%	9 23% 12%-38%	8 20% 11%-35%
SC/SA verified self-reported quitter	1 3% 0%-13%	1 3% 0%-13%	-	4 10% 4%-23%	7 18% 9%-32%	8 20% 11%-35%	-	6 15% 7%-29%
eCO and SC/SA verified self-reported quitter	1 3% 0%-13%	0 0% 0%-9%	-	4 10% 4%-23%	7 18% 9%-32%	8 20% 11%-35%	-	6 15% 7%-29%
RS6-eCO	-	-	-	2 5% 1%-17%	-	-	-	6 15% 7%-29%
RS6-S	-	-	-	1 3% 0%-13%	-	-	-	4 10% 4%-23%)

Table 3.37 Smoking outcome measures- binary.

Outcome Min Median (LQ-UQ) Mean (SD) Max 95% CI	Control Group, n=40			Intervention Group, n=40		
	Change from baseline to 4 weeks	Change from baseline to 3 months	Change from baseline to 6 months	Change from baseline to 4 weeks	Change from baseline to 3 months	Change from baseline to 6 months
FTND	-9	-9	-8	-8	-8	-7
	-1 (-3 to 0)	-1 (-3 to 0)	-1 (-2 to 0)	-2 (-4 to -1)	-3 (-4 to -1)	-2 (-3 to 0)
	-2 (2.5)	-2 (2.4)	-2 (2.1)	-2 (2.3)	-3 (2.1)	-2 (2.0)
	2	3	1	2	1	1
	-2.7 to -1.0	-2.7 to -0.9	-2.4 to -0.8	-3.2 to -1.6	-3.5 to -2.0	-2.7 to -1.2
MPSS	-29	-24	-26	-17	-17	-18
	-2 (-4 to 1)	-3 (-6 to 0)	-3 (-7 to 2)	-0.5 (-5 to 2)	-3 (-7 to 2)	-3 (-8 to 0)
	-3 (6.2)	-4 (7.4)	-3 (8.3)	-2 (5.5)	-3 (6.3)	-3 (8.8)
	7	7	12	9	9	34
	-5 to -0.5	-6.4 to -1.0	-6.0 to 0.3	-4.0 to 0.0	-5.3 to -0.8	-6.1 to 0.6
eCO	-49	-49	-47	-33	-33	-34
	2 (-6 to 7)	-3 (-11 to 0)	-4 (-11 to 2)	-12 (-20 to -4)	-12 (-23 to -3)	-12 (-20 to -5)
	-1 (13)	-6 (11.9)	-6 (12.3)	-12 (10.3)	-13 (11.0)	-12 (11.0)
	35	14	16	8	6	8
	-6 to 4	-10 to -2	-10 to -1	-15 to -8	-17 to -9	-16 to -8
SC	-224	-	-457	-297	-	-500
	10 (-27 to 57)		-15 (-66 to 33)	-70 (-124 to 2)		-66 (-111 to 27)
	12 (80.2)		-37 (133)	-64 (113)		-62 (132)
	283		147	230		164
	-17 to 40		-90 to 16	-104 to -23		-112 to -12
SA	-1.8	-	-1.8	-4.5	-	-5.0
	0 (-0.3 to 0.2)		0.1 (-0.1 to 0.4)	-0.4 (-0.8 to 0)		-0.2 (-0.9 to 0.2)
	0 (0.8)		0.5 (2.3)	-0.4 (1.9)		-0.4 (1.2)
	2.4		11.6	8.0		1.7
	-0.3 to 0.3		-0.5 to 1.4	-1.1 to 0.3		-0.9 to 0

Table 3.38 Change in smoking outcome measures between visits.

Fagerstroms test of nicotine dependence

The mean FTND score at baseline for both groups was five, indicating moderate nicotine dependence. The FTND reduced by two units in both groups during the six months of the study, denoting a reduction in nicotine dependence. Figure 3.27 presents the FTND by randomisation group at five time points.

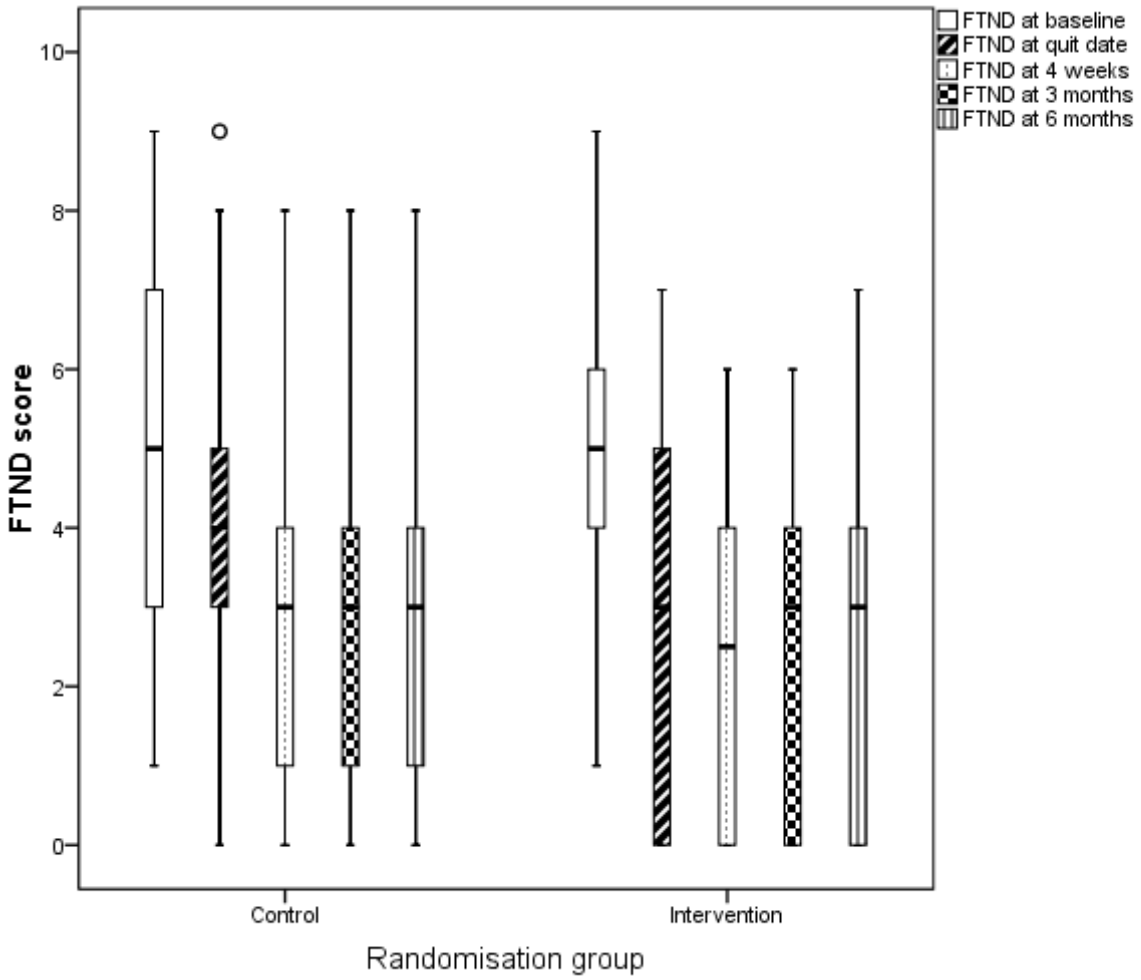

Figure 3.27 FTND by randomisation at baseline, quit date, 4 weeks, 3 months and 6 month.

Boxplot representing five-number summary: minimum value that is no greater than 1.5 times the IQR (lower whisker), 25th percentile (bottom of box), median (dark line in middle), 75th percentile (top of box) and maximum value that is no greater than 1.5 times IQR (upper whisker). Mild outliers (open circles) are values between 1.5 and 3 times the IQR. Extreme outliers (asterisks) are values more than 3 times the IQR.

Mood and physical symptoms scale

The mean MPSS score at baseline for both groups was 23. The MPSS scores are largely similar between the groups at the different time points, indicating they experienced similar withdrawal symptoms. At 4 weeks, 3 months and 6 months both groups demonstrated similar reductions in the MPSS score. Figure 3.28 presents the MPSS scores by randomisation group at five time points.

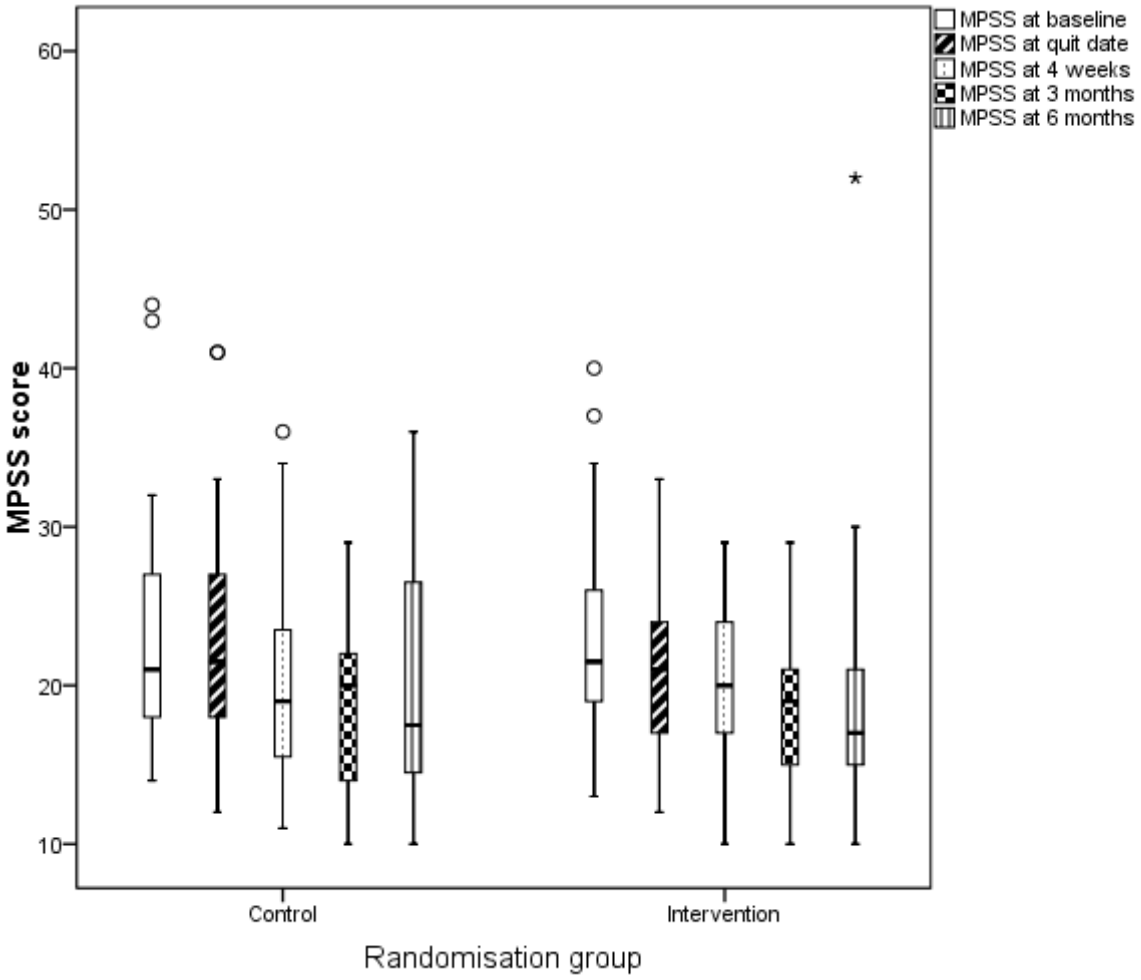

Figure 3.28 MPSS by randomisation group at baseline, quit date, 4 weeks, 3 months and 6 months.

Boxplot representing five-number summary: minimum value that is no greater than 1.5 times the IQR (lower whisker), 25th percentile (bottom of box), median (dark line in middle), 75th percentile (top of box) and maximum value that is no greater than 1.5 times IQR (upper whisker). Mild outliers (open circles) are values between 1.5 and 3 times the IQR. Extreme outliers (asterisks) are values more than 3 times the IQR.

Expired air carbon monoxide measure

The intervention group presented with a higher baseline eCO reading compared to the control group (23 ppm versus 18 ppm). The eCO reduced in both groups during the study. The control group had a 6 ppm reduction in eCO over the 6 months of the study, with the largest reduction occurring between 4 weeks and 3 months. The intervention group had a 12 ppm reduction in eCO over the 6 months of the study, with this all occurring by the 4-week time point and being maintained. Figure 3.29 presents the eCO by randomisation group at five time points.

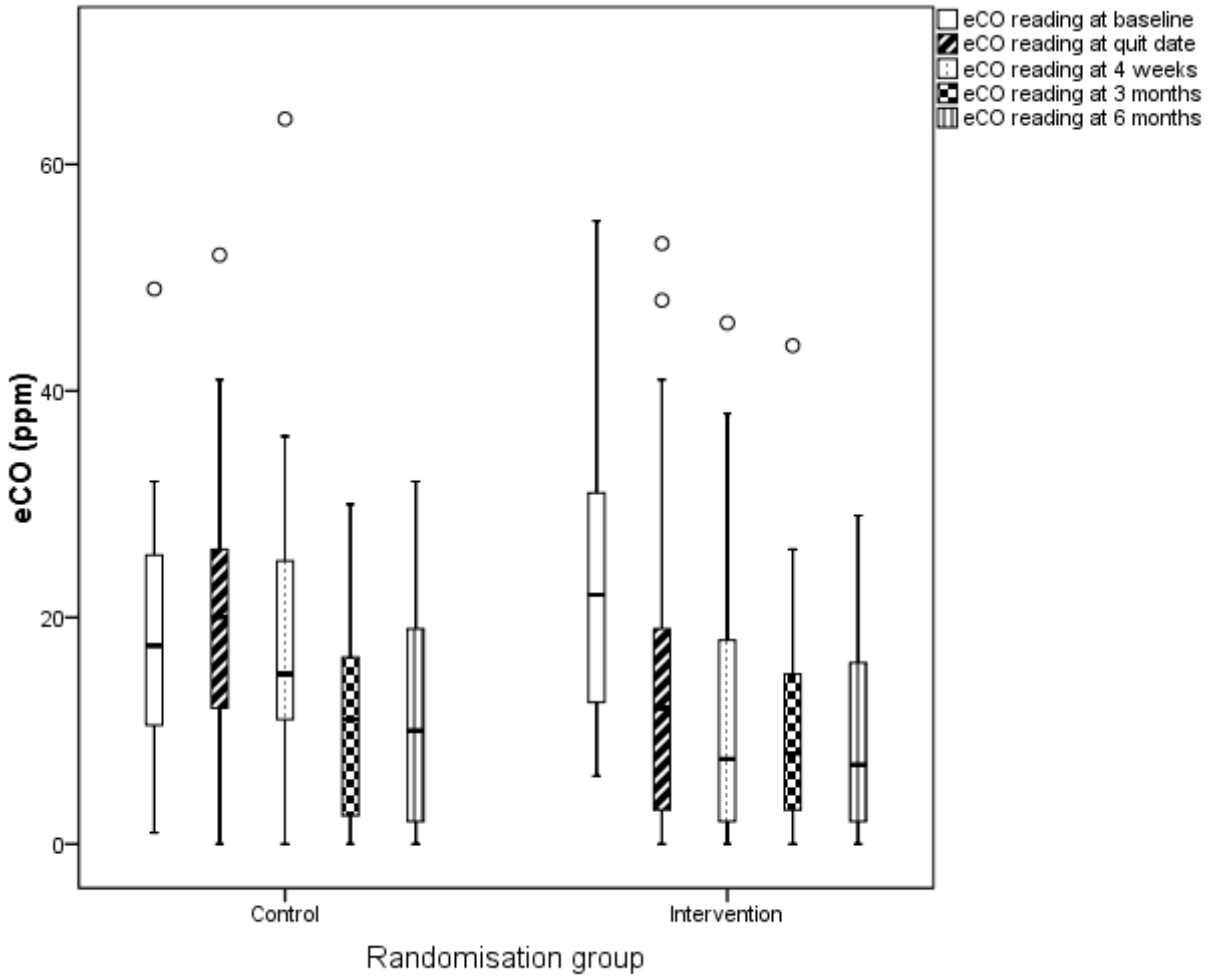

Figure 3.29 eCO by randomisation group at baseline, quit date, 4 weeks, 3 months and 6 months.

Boxplot representing five-number summary: minimum value that is no greater than 1.5 times the IQR (lower whisker), 25th percentile (bottom of box), median (dark line in middle), 75th percentile (top of box) and maximum value that is no greater than 1.5 times IQR (upper whisker). Mild outliers (open circles) are values between 1.5 and 3 times the IQR. Extreme outliers (asterisks) are values more than 3 times the IQR.

Salivary cotinine and anabasine analysis

The salivary cotinine concentration was slightly higher in the intervention group at baseline (343 ng/ml versus 303 ng/ml). The intervention group had a reduction in salivary cotinine concentration at both the 4-week and 6-month time points (64 ng/ml and 62 ng/ml respectfully), indicating they had reduced their nicotine intake (from any source; tobacco, NRT or e-cigarettes). The control group had a small increase in salivary cotinine concentration at 4 weeks (12 ng/ml), followed by a reduction at 6 months (37 ng/ml), indicating they had reduced their nicotine intake by the end of the study. Figure 3.30 presents the salivary cotinine concentrations by randomisation group at four time points.

The salivary anabasine concentration was similar between the groups at baseline, 1.1 ng/ml in the control group and 1.2 ng/ml in the intervention group. The intervention group had a reduction in salivary anabasine concentration of 0.4 ng/ml at both the 4-week and 6-month time point, indicating a reduction in tobacco smoking. The control group showed no change in salivary anabasine concentration at 4 weeks and an increase of 0.5 ng/ml at 6 months, indicating an increase in tobacco smoking. This appears to be in contrast to the previously detailed reduction of nicotine. Possible explanations include that there was no real difference (no statistical testing has been performed), this was the effect of an extreme outlier in the control group at 6 months (see Figure 3.31) or that there was a complex change in smoking behaviour i.e. increased exposure to tobacco metabolites could have occurred from compensatory smoking when participants reduced the number of cigarettes they smoked (self-reported cigarettes per day reduced from a mean of 17 to 9 throughout the study). Figure 3.31 presents the salivary anabasine concentrations by randomisation group at four time points.

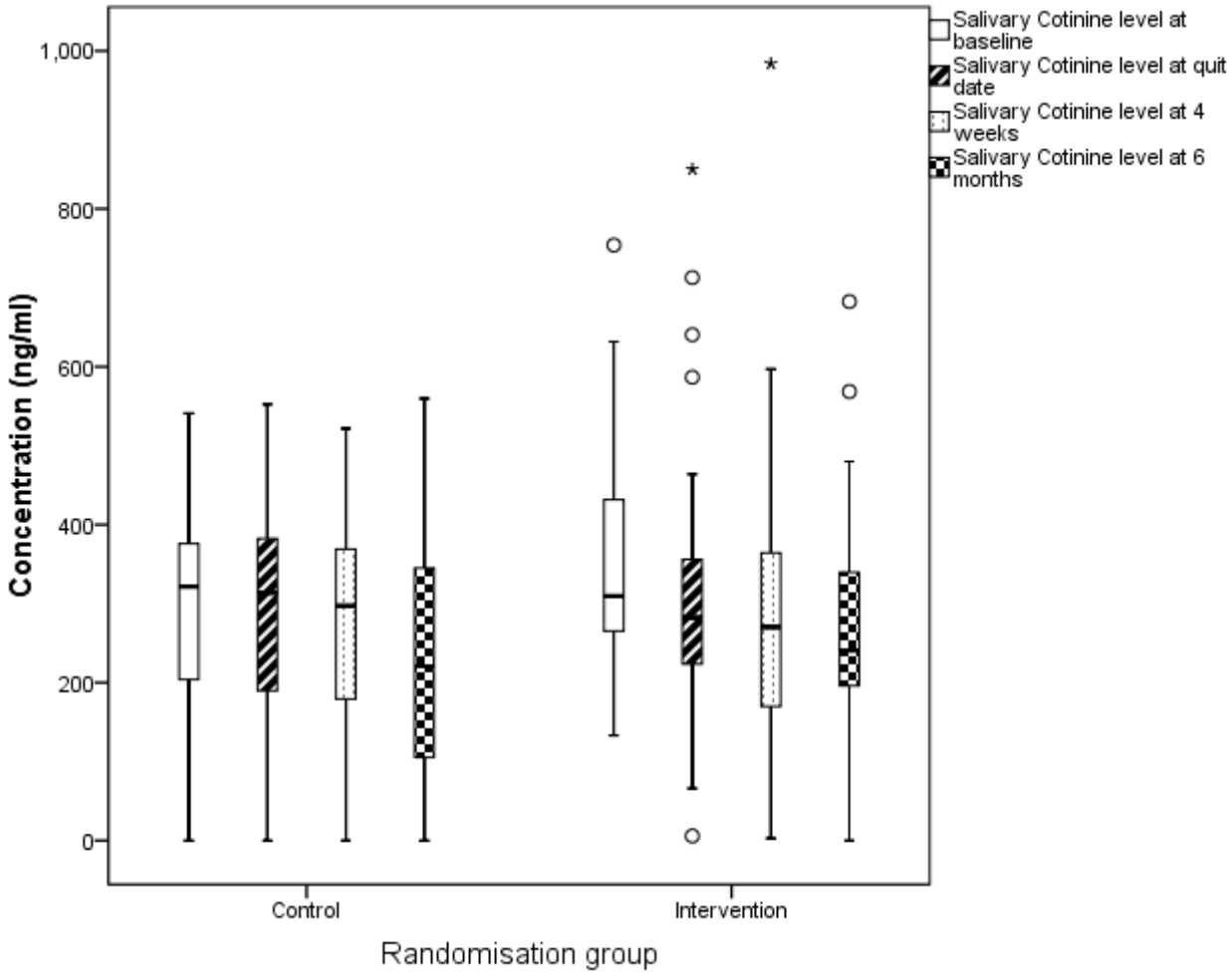

Figure 3.30 Salivary cotinine concentration by randomisation group at baseline, quit date, 4 weeks and 6 months.

Boxplot representing five-number summary: minimum value that is no greater than 1.5 times the IQR (lower whisker), 25th percentile (bottom of box), median (dark line in middle), 75th percentile (top of box) and maximum value that is no greater than 1.5 times IQR (upper whisker). Mild outliers (open circles) are values between 1.5 and 3 times the IQR. Extreme outliers (asterisks) are values more than 3 times the IQR.

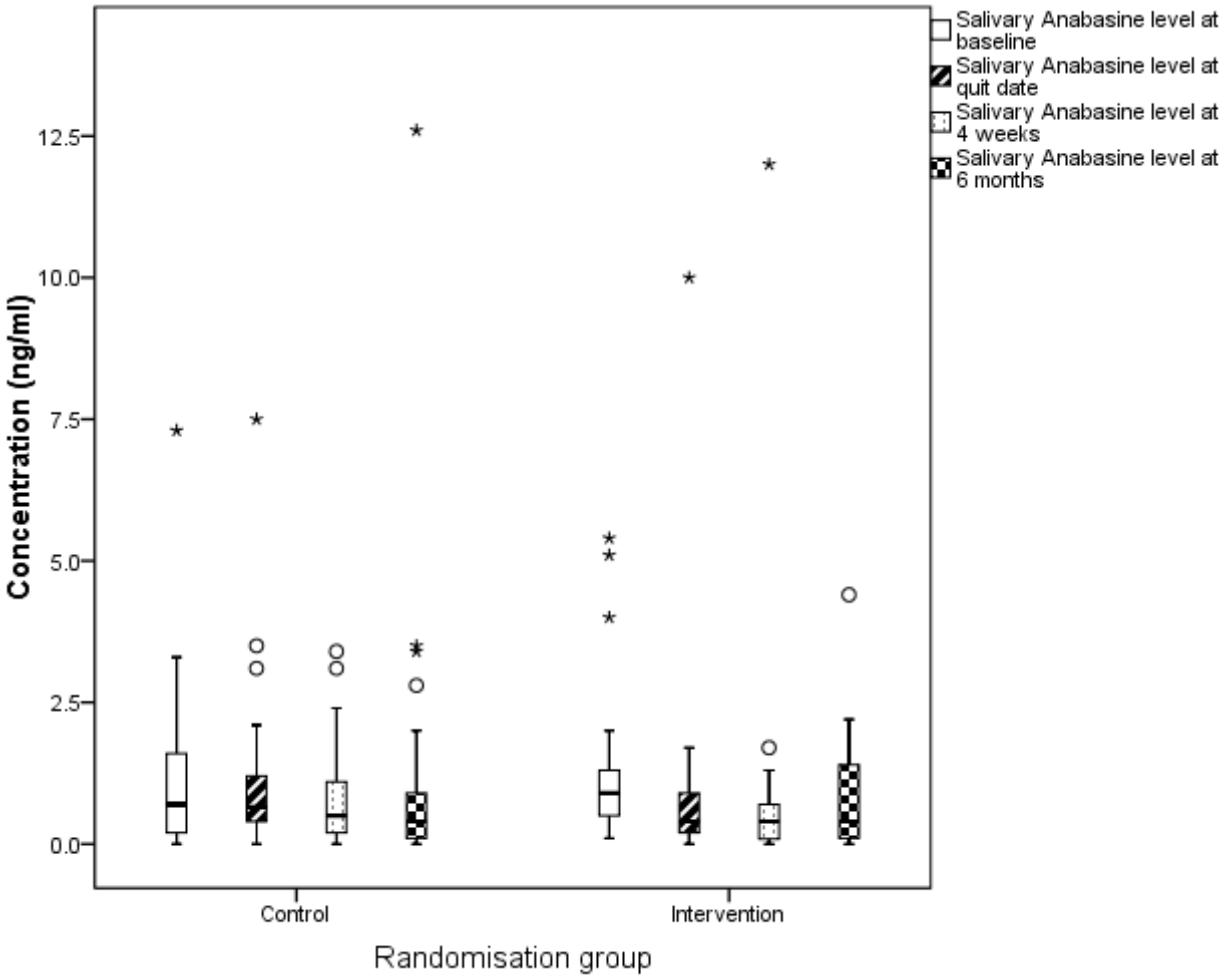

Figure 3.31 Salivary anabasine concentration by randomisation group at baseline, quit date, 4 weeks and 6 months.

Boxplot representing five-number summary: minimum value that is no greater than 1.5 times the IQR (lower whisker), 25th percentile (bottom of box), median (dark line in middle), 75th percentile (top of box) and maximum value that is no greater than 1.5 times IQR (upper whisker). Mild outliers (open circles) are values between 1.5 and 3 times the IQR. Extreme outliers (asterisks) are values more than 3 times the IQR.

Self-reported number of cigarettes (any type) per day

At baseline, the number of cigarettes smoked per day was 17 in both groups, based on participants' self-reporting. The number of cigarettes smoked throughout the study decreased in both groups. The intervention group had an initial rapid decrease at the quit date which was largely maintained throughout the study period. The control group had a more gradual reduction throughout the study and by 6 months both groups had comparable levels. Figure 3.32 presents the self-reported number of cigarettes per day, for all participants, at five time points.

When limiting the analysis to those still smoking, similar patterns were seen, with both groups reporting 11 cigarettes/day at 6 months. Figure 3.33 presents the self-reported number of cigarettes per day, for those still smoking, at five time points.

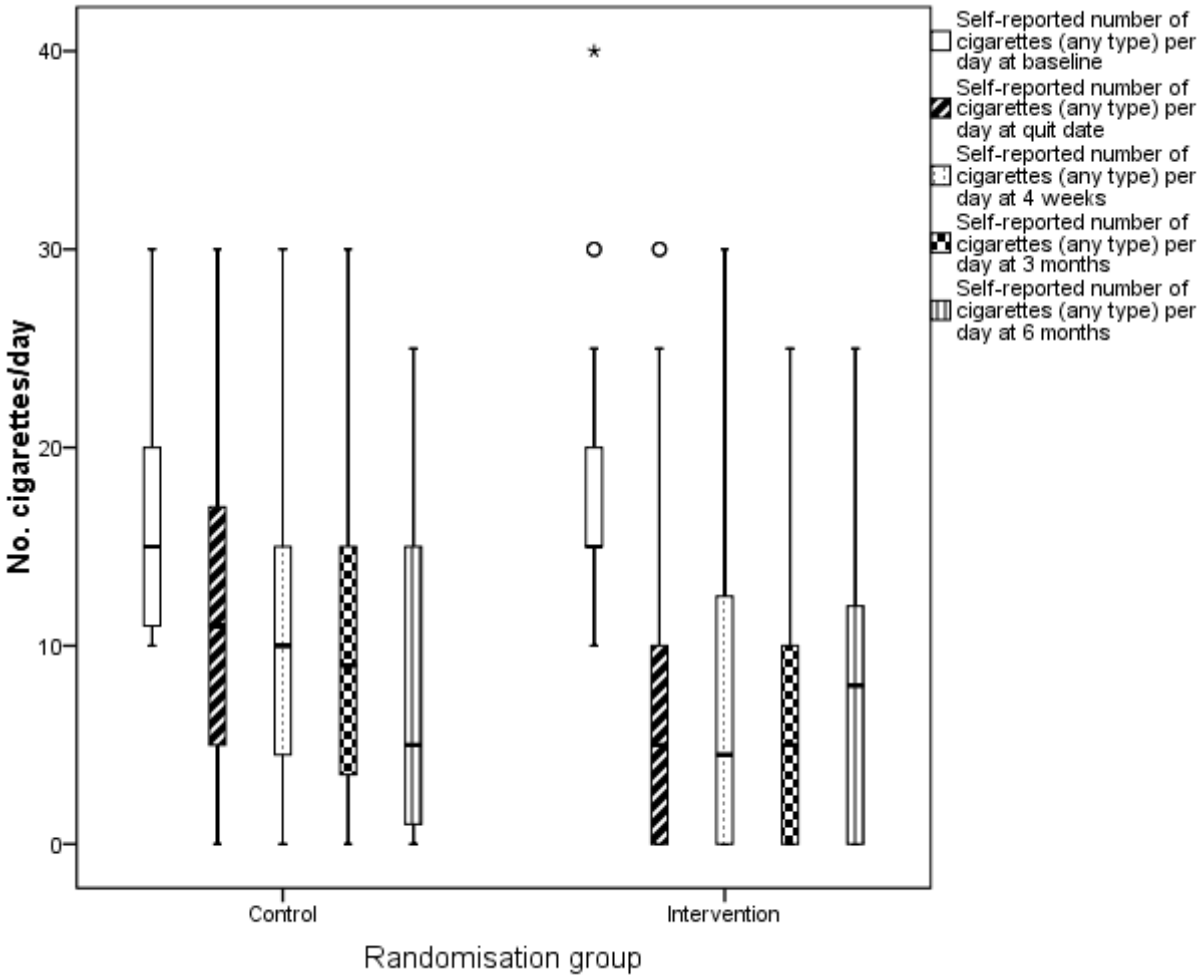

Figure 3.32 Self-reported number of cigarettes per day for all participants (any type).

Boxplot representing five-number summary: minimum value that is no greater than 1.5 times the IQR (lower whisker), 25th percentile (bottom of box), median (dark line in middle), 75th percentile (top of box) and maximum value that is no greater than 1.5 times IQR (upper whisker). Mild outliers (open circles) are values between 1.5 and 3 times the IQR. Extreme outliers (asterisks) are values more than 3 times the IQR.

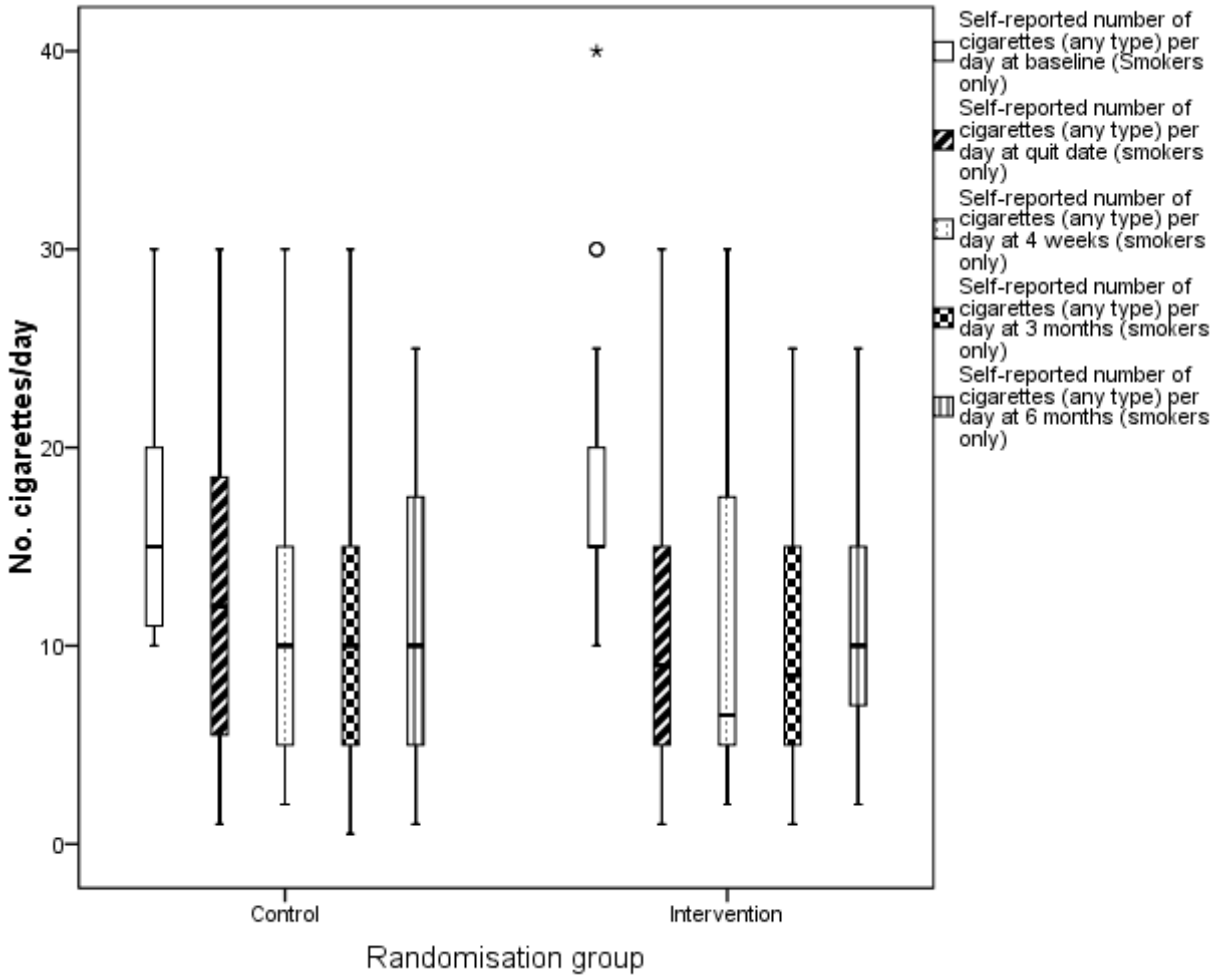

Figure 3.33 Self-reported number of cigarettes per day for those still smoking (any type).

Boxplot representing five-number summary: minimum value that is no greater than 1.5 times the IQR (lower whisker), 25th percentile (bottom of box), median (dark line in middle), 75th percentile (top of box) and maximum value that is no greater than 1.5 times IQR (upper whisker). Mild outliers (open circles) are values between 1.5 and 3 times the IQR. Extreme outliers (asterisks) are values more than 3 times the IQR.

Smoking abstinence

Smoking abstinence was assessed by several different methods in this study. These comprised self-reporting and biochemical validation with eCO and salivary analysis. Six different measures of smoking abstinence, of increasing strictness, are presented in Table 3.37. Across all the measures there were more quitters in the intervention group at all time points. The number of quitters reduced with the increasing strictness of the smoking abstinence measure i.e. overall there were 12 self-reported quitters at 6 months but this reduced to 8 following application of the RS6-eCO and 5 following application of the RS6-S. Generally there was good agreement between the two biochemical assessments of tobacco intake (eCO and salivary analysis). Across the three follow-up visits at where both eCO and saliva were collected (quit date, 4 weeks and 6 months) there was agreement on 26 self-reported quit statuses and disagreement on 9. All the disagreements involved the salivary analysis being more strict and classifying the participant as a smoker, when the eCO analysis had not. This is likely to be due to the longer half-life of the salivary biomarkers and hence the increased sensitivity of the salivary analysis to detect previous smoking within 3-5 days compared to 12-24 hours for eCO.

Using RS6-eCO, there were two quitters in the control group giving a cessation rate of 5% [95% CI: 1%-17%] and six in the intervention group giving a cessation rate of 15% [95% CI: 7%-29%]. Non-attenders are counted as smokers as per the Russel Standard (West *et al.*, 2005b). Both the RS6-eCO quitters in the control group reported using an e-cigarette as part of their quit attempt. One of these participants used an e-cigarette for the whole duration of the study whilst the other used it for the first part of the study, stopping after the 4-week visit.

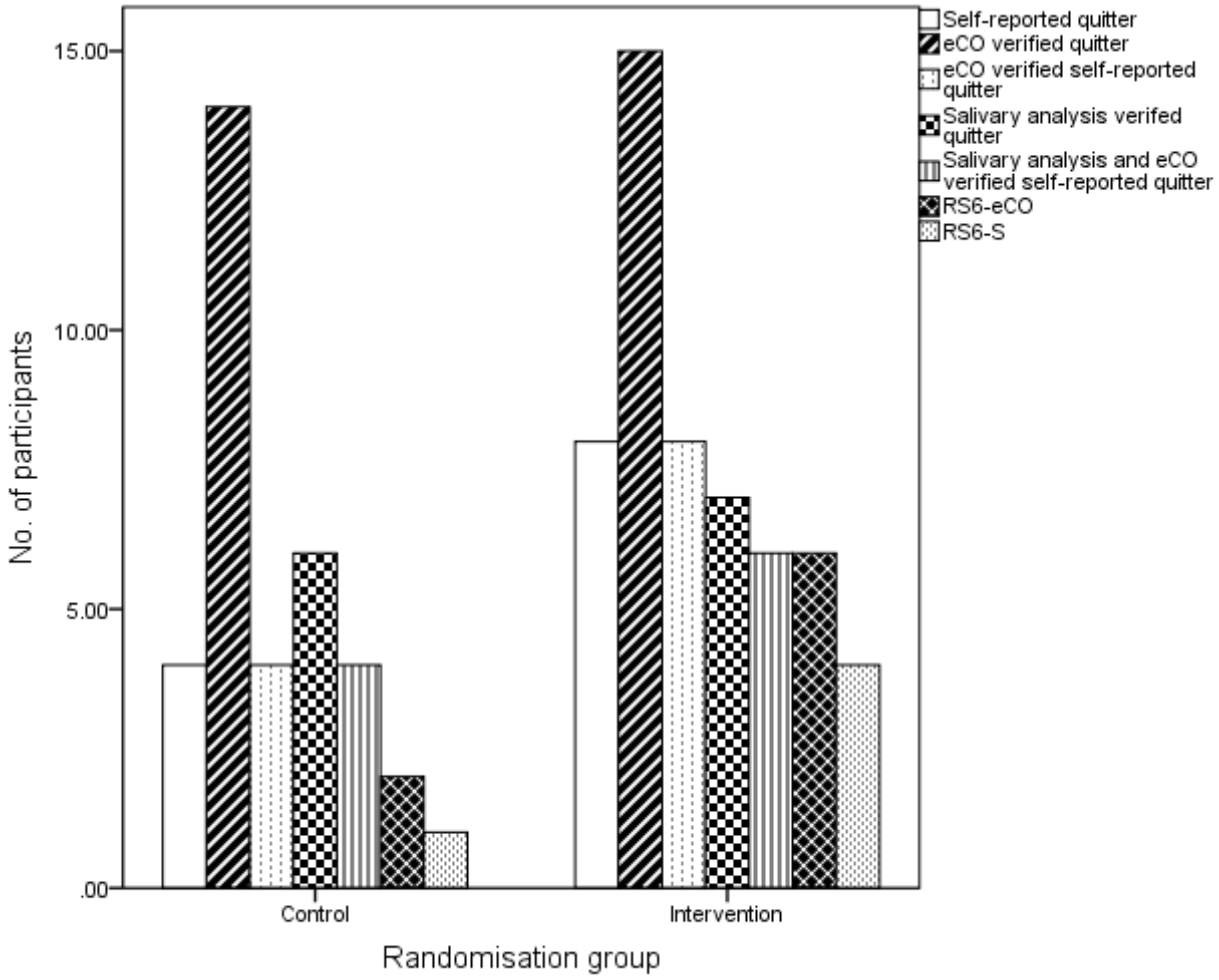

Figure 3.34 Smoking abstinence measures at 6 months by randomisation group.

3.5.15 *Data completeness*

Overall excellent data completeness was achieved across the outcome measures used in this study for those followed up. Most measures achieved 100% completeness at all time points as detailed in Table 3.40. There were a small number of instances where data could not be collected for clinical reasons (e.g. not enough healing time had elapsed following treatment) and due to incomplete questionnaire completion (two instances). All of the OHQoL-UK questionnaires were complete with no missing items (these were self-completed in clinic with a research dental nurse checking for completeness). All of the FTND questionnaires were partially or fully completed with 1% of baseline questionnaires having one missing item. All of the MPSS questionnaires were partially or fully completed with 1% of baseline questionnaires having 5 missing items, 4% of visit 2 questionnaires having one missing item, 2% of visit 6 questionnaires having one item missing and 2% of visit 6 questionnaires having two items missing. No patterns were present with regards to the missing items.

In total, 281 saliva samples were collected. Three saliva samples, from three participants, had an insufficient volume for laboratory analysis. One saliva sample could only have partial laboratory analysis (SC and not SA) due to an insufficient volume. All of these were collected at the start of the study, all within the first ten saliva samples collected, indicating there may have been a procedural error.

One participant declined for his samples (saliva, GCF or subgingival plaque) to be transferred outside of the European Economic Area (EEA), specifically requesting his samples were not processed in the USA (the subgingival plaque samples were originally planned to be processed in the USA but this was later revised to a UK-based laboratory).

PPD data were carried forwards between visit 5 and 6 for four participants on five teeth. The mean (SD) of the carried forwards PPD data was 4.5 mm (1.6). Table 3.39 provides details of the carried forwards data by randomisation group.

	Control group *n*=3	Intervention group *n*=2	Total *n*=5
Mean (SD) PPD (mm) of data carried forwards between visit 5 and 6	4.8 (1.8)	4.1 (1.3)	4.5 (1.6)

Table 3.39 Summary of PPD data carried forwards between visit 5 (3 months) and visit 6 (6 months).

Data element	Visit	Consented for procedure	Completed procedure/ data collected	Data completeness	Comment
Pocket Probing Depths	Baseline	80	80	100%	1030- Data not collected from three teeth. The indices were being taken alongside the patient's treatment under local anaesthetic due to anxiety. They failed to attend part way through these sessions hence the data incompleteness.
	Visit 5	64	61	95%	1040, 1048, 1058- Oral health indices not collected on three participants at visit 5. This is because their periodontal treatment had extended beyond the original 2 visits or had been delayed, meaning not enough healing time has elapsed following the treatment to collect the indices. Smoking outcome data was still collected.
	Visit 6	58	58	100%	
Gingival Index	Baseline	80	80	100%	See comments in PPD comments above
	Visit 5	64	61	95%	See comments in PPD comments above
	Visit 6	58	58	100%	
Plaque Index	Baseline	80	80	100%	See comments in PPD comments above
	Visit 5	64	61	95%	See comments in PPD comments above
	Visit 6	58	58	100%	
Bleeding on Probing	Baseline	80	80	100%	See comments in PPD comments above
	Visit 5	64	61	95%	See comments in PPD comments above
	Visit 6	58	58	100%	
	Baseline	80	80	100%	See comments in PPD comments above
	Visit 5	64	61	95%	See comments in PPD comments above

Data element	Visit	Consented for procedure	Completed procedure/ data collected	Data completeness	Comment
Clinical Attachment Loss	Visit 6	58	58	100%	
Clinical Oral Dryness Score	Baseline	80	80	100%	
	Visit 5	64	61	95%	See comments in PPD comments above
	Visit 6	58	58	100%	
Expired air Carbon Monoxide	Baseline	80	80	100%	
	Visit 2	76	75	99%	Carbon monoxide machine failure (1046)
	Visit 4	67	66	99%	Carbon monoxide machine failure (1006)
	Visit 5	64	64	100%	
	Visit 6	58	58	100%	
Saliva sample	Baseline	80	80	100%	
	Visit 2	76	76	100%	
	Visit 4	67	67	100%	
	Visit 5	64	64	100%	
	Visit 6	58	58	100%	
Subgingival plaque sample	Baseline	80	80	100%	
	Visit 2	76	76	100%	
	Visit 5	64	61	95%	See comments in PPD comments above
	Visit 6	58	58	100%	
Gingival crevicular fluid sample	Baseline	80	80	100%	
	Visit 5	64	61	95%	See comments in PPD comments above
	Visit 6	58	58	100%	
Fagerstrom Test for Nicotine Dependence (6 items)	Baseline	80	80	100%	
	Visit 2	76	76	100%	
	Visit 4	67	67	100%	
	Visit 5	64	64	100%	
	Visit 6	58	58	100%	

Data element	Visit	Consented for procedure	Completed procedure/ data collected	Data completeness	Comment
Mood and Physical Symptoms Scale (12 items in three subsections with 7,2,3 questions)	Baseline	80	80	100%	Participant 1021 missed 5 items from this questionnaire so has been classed as missing in data analysis.
	Visit 2	76	76	100%	
	Visit 4	67	67	100%	
	Visit 5	64	64	100%	
	Visit 6	58	57	99%	Participant 1071 missed two items from this questionnaire. Following the 'rule of halves' it was not possible in impute means, as more than half of the subsection was missing, and the whole questionnaire was classed as missing.
Oral Health Quality of Life Questionnaire (16 items)	Baseline	80	80	100%	
	Visit 6	58	58	100%	

Table 3.40 Data completeness.

3.5.16 *Definitive study sample size calculation*

One of the objectives of this pilot trial was to collect estimates of the variables and parameters required to inform a definitive study sample size calculation.

There are two important outcomes of the e-cigarette intervention under investigation: smoking abstinence rates and periodontal health. Therefore, I propose that the future definitive study should have co-primary outcomes and be powered accordingly.

For the smoking abstinence outcome measure, I propose to use Russell Standard 6-month sustained abstinence, defined as self-report of smoking no more than five cigarettes in the previous 6 months and not smoking in the previous week, verified by an eCO reading below 10 ppm. A control group rate of smoking abstinence at 6 months of 7% was used based on previous research (Carr and Ebbert, 2012) and in keeping with the rate seen in this pilot study (5%, 95% CI: 1%-17%). Minimally clinically important differences (MCIDs) have previously been reported in the range of 6% to 10% (West *et al.*, 2010; Bullen *et al.*, 2013; Caponnetto *et al.*, 2013; Stapleton *et al.*, 2013; Lindson-Hawley *et al.*, 2014; Hajek *et al.*, 2015c; Sarkar *et al.*, 2017), with 10% being used most recently by e-cigarette studies (Bullen *et al.*, 2013; Caponnetto *et al.*, 2013; Stapleton *et al.*; Hajek *et al.*, 2015c).

In keeping with the Russell Standard (West *et al.*, 2005b), and recent studies (Tappin *et al.*, 2012; Hajek *et al.*, 2015c), sample sizes are not required to be inflated to allow for attrition, as those who are lost to follow-up are included in the analysis as smokers. However, this approach has recently been challenged (Jackson *et al.*, 2014), with recommendations that sensitivity analysis also be completed (with inflation for attrition) around the assumption that lost to follow-up are counted as smokers. Table 3.41 presents four scenarios in which either an 8% or 10% MCID has been used, with or without inflation for attrition. Scenario 4 is unlikely to be practicable.

Scenario	MCID	Inflate for attrition?	Total consented and randomised participants	Total potential participants needed to be approached
1	10	No	466	804
2	10	Yes	640	1104
3	8	No	674	1162
4	8	Yes	924	1594

Table 3.41 Sample size scenarios

Scenario 3 has been used in this sample size calculation; in order to detect an 8% difference in 6-month smoking abstinence rates between intervention arms, with a control group rate of 7% (90% power, 5% significance level, two-sided test) 337 participants will be required per arm, 674 in total (Dobson and Gebski, 1986). Given any randomised participants who are lost to follow-up will be included in the ITT analysis of smoking abstinence as smokers at 6 months, this sample size has not been adjusted for attrition. However, the consent rate amongst those eligible in the pilot trial was 67%, (95% CI: 58%-75%). Given that the definitive study will be conducted in multiple centres and the pilot trial was conducted in a single centre (and as part of a doctoral fellowship), it would be prudent to use the lower bound of this 95% CI and on this basis, the future definitive study would need to approach 1162 potentially eligible patients in order to consent and randomise 674.

For the periodontal health outcome measure there are several potential outcome measures that could be used. Whole mouth mean PPD is often used, despite not being the best method to assess clinical significance (Addy and Newcombe, 2005). This calculation uses a MCID of 0.25 mm in line with previous research (Preshaw *et al.*, 2004). Pooled standard deviations of the change from baseline to 6 months for the outcome measures assessed in the pilot trial are presented in Table 3.42. For PPD the pooled standard deviation was 0.56mm. Therefore, to detect a difference between intervention arms in the mean change from baseline in PPD of 0.25 mm (pooled standard deviation of 0.56 mm, 90% power, 5% significance level, two-sided test) 107 participants will be required per arm, 214 in total (Julious, 2010).

Assessing the proportion of healthy or diseased sites may be a more relevant measure of clinical significance. A PPD of 4 mm is often used as a threshold as pockets ≤4 mm are

manageable by the clinician and patient, and pockets ≥5 mm have a poorer long-term prognosis (Lang and Tonetti, 2003; Matuliene *et al.*, 2008). Proportionally large differences between groups, of 25-50%, are probably required for clinical significance (Addy and Newcombe, 2005). The pooled standard deviation of the change in the percentage of diseased sites (PPD ≥5 mm) from the pilot trial was 13.5%, and the observed mean reduction from baseline in the control group was 19.0% (which is in line with other studies (Preshaw *et al.*, 2013)). To detect a relative 25% difference in the mean reduction in the percentage of diseased sites, 19% versus 23.75% (pooled standard deviation 13.5%, 90% power, 5% significance level, two-sided test) 171 participants will be required per arm, 342 in total.

Both of the sample sizes calculated for these periodontal outcome measures (mean PPD and percentage of diseased sites) are less than the sample size calculated for smoking abstinence (n=674 in total).

Taking into account the participant retention rate observed in the pilot trial (73%, 95% CI: 62%-81%), PDD data at 6 months would be expected to be available for approximately 492 participants. Using the same standard deviations as in the PDD sample size calculations above, it can be calculated that, a 0.16 mm difference between intervention arms in the mean change in PPD and a 21% relative difference in percentage of diseases sites would be detectable with PDD data on 246 participants per arm.

The sample size calculations were performed using the *proc power twosamplemeans and twosamplefreq* procedures in SAS version 9.4 of the SAS System for Windows 7, copyright © 2012 SAS Institute Inc.

Parameter	Pooled standard deviation
3 month change in mean PPD	0.51
6 month change in mean PPD	0.55
3 month change in mean PPD [mm] of those sites with a baseline PPD ≥5 mm	0.65
6 month change in mean PPD [mm] of those sites with a baseline PPD ≥5 mm	0.65
3 month change in mean PPD [mm] of those sites with a baseline PPD ≥6 mm	1.00
6 month change in mean PPD [mm] of those sites with a baseline PPD ≥6 mm	0.96
3 month change in mean PPD [mm] of those sites with a baseline PPD ≥7 mm	1.20
6 month change in mean PPD [mm] of those sites with a baseline PPD ≥7 mm	1.36
3 month change in mean PPD [mm] of those sites with a baseline PPD ≤4 mm	0.30
6 month change in mean PPD [mm] of those sites with a baseline PPD ≤4 mm	0.35
3 month change in percentage of sites with PPD ≥5 mm	13.96
6 month change in percentage of sites with PPD ≥5 mm	13.51
3 month change in percentage of sites with PPD >6 mm	7.70
6 month change in percentage of sites with PPD >6 mm	7.46
3 month change in mean MGI	0.35
6 month change in mean MGI	0.50
3 month change in mean PI	0.45
6 month change in mean PI	0.45
3 month change in meal CAL	0.70

Parameter	Pooled standard deviation
6 month change in mean CAL	0.81
3 month change in % BOP score	12.67
6 month change in % BOP score	13.55
3 month change in CODS	1.80
6 month change in CODS	1.46
3 month change in PESA [mm^2]	383.04
6 month change in PESA [mm^2]	396.23
3 month change in PISA [mm^2]	468.09
6 month change in PISA [mm^2]	461.00
6 month change in OHQoL-UK	14.29

Table 3.42 Pooled standard deviations for periodontal outcome measures.

3.5.15 Feasibility outcomes

There were a number of feasibility trial objectives assessed in this study. The outcomes of these are presented in Table 3.43.

Trial objective	Outcome
To estimate the eligibility rates among our patient population.	Could only be assessed for periodontal new patient clinic recruitment source: 29 eligible participants were identified from 391 patients giving a 7.4% eligibility rate [95% CI: 5.2%-10.5%]. (Unable to make any estimates beyond this.)
To assess patients' willingness to enter the trial.	80 participants were consented from 119 potentially eligible patients (67%).
To estimate the recruitment rate; can 80 eligible patients be recruited in a 12-month period?	Unable to recruit within 12 months but successfully completed within 15 months. Average recruitment rate was 5.3/month.
To ascertain the retention rate of the participants for 6-month follow-up data.	58 participants completed the study (reaching the 6-month follow-up visit) giving a retention rate of 73% [95% CI: 62%-81%].
To ascertain the randomised group contamination rates (i.e. the extent of cross-over between the two arms of the trial).	20% [95% CI: 11%-35%] of those in control group reported using an e-cigarette at some point in the study. One participant (3%) reported using an e-cigarette at all follow-up time points.
To test a weekly smoking status data collection method.	Generally poorly completed by participants with only 46% of participants completing it more than half of the time.

Trial objective	Outcome
To compare descriptively novel and traditional periodontal outcome measures. (Novel: PISA, PESA. Traditional: PPDs.)	See section 3.5.12. The traditional and novel periodontal outcome measures gave comparable results (not surprising).
To estimate the standard deviation of the periodontal outcome measures to input to the sample size calculation for future definitive trials.	See section 3.5.16 and Table 3.42.
To test the collection of subgingival plaque for microbiome analysis.	Successfully collected 100% of samples at baseline and 6 months, and 95% of samples at 3 months (of those who attended these visits).
To test the collection of GCF for inflammatory biomarker analysis.	Successfully collected 100% of samples at baseline and 6 months, and 95% of samples at 3 months (of those who attended these visits).
To ascertain participant compliance when provided with an e-cigarette.	- 39 (98%, 95% CI: 87%-100%) participants accepted the intervention. - 36 (90%, 95% CI: 77%-96%) participants using at quit date. - 31 (78%, 95% CI: 63%-88%) participants using at 4 weeks. - 28 (70%,95% CI: 53%-83%) participants using at 3 months.

Trial objective	Outcome
	- 21 (53%, 95% CI: 38%-67%) participants using at 6 months.
To describe tobacco smoking and e-cigarette usage.	See section 3.5.14 smoking outcome measures for a detailed description of these data.
To ascertain participant behaviour regarding the use of the e-cigarette: straight nicotine replacement or nicotine cessation device?	10-18% of participants chose to use non-recommended brands of e-liquids at the different follow up points. These participants made up the vast majority of the quitters in the intervention group. Further exploration of e-cigarette perceptions in chapter 5.
To complete a Qualitative Process Evaluation to establish the views of participants on the provision of e-cigarettes and to finalise the exact characteristics of an e-cigarette intervention for the future definitive study for this patient group.	See chapter 5.

Table 3.43 Feasibility outcomes.

3.6 **Discussion**

3.6.1 ***Main findings***

Recruitment, interventions and retention to the study

The study achieved its target of recruiting 80 patients who were smokers, suffering from periodontitis, who had recently attended a dentist. Patients were recruited from a variety of sources including primary and secondary care environments. The vast majority of the patients identified to the research team by recruiting sources were found to be eligible, probably due to the broad nature of the eligibility criteria and diligent work of those identifying. However, approximately a third of the patients identified did not go on to participate in the study for a variety of personal reasons and by failing to attend baseline appointments. PICs had a particularly low conversion rate with less than half of identified patients going onto participate in the study, while the DEC had a two-thirds conversion rate, and the periodontal new patient clinic had an 83% conversion rate.

The smoking cessation interventions were well accepted by the participants. Only one participant in the intervention group declined to accept the e-cigarette starter kit. Adherence to the e-cigarette intervention was good with the majority (90%) of the participants in the control group using the e-cigarette at the quit date, 78% at 4 weeks, and 53% at 6 months. There was a moderate level of e-cigarette use by the control group despite participants being asked to refrain from e-cigarette use. Participants in the intervention group who deviated from recommendations and used non-recommended brands of e-liquid, appeared to achieve higher quit rates (although statistical testing was not completed).

The periodontal treatment was successfully delivered to all participants, usually using the FMD approach over two visits. However, in a small number of participants (3), due to clinical need or patient anxiety, the treatment was delivered in a quadrant-wise approach (over 3 or 4 visits). For three participants we were unable to collect oral health indices at the 3-month visit as there had been insufficient healing time period following the completion of the treatment (smoking outcome data was collected, however).

Participant retention to the study was moderate with 73% of the participants completing the study; rates of retention were the same for the control and intervention groups. Each visit had a designated study window and compliance with these was mixed. At the 4-week time point, 11% of participants attended outwith the study period (16% FTA); the corresponding value at the 6-month time point was 9% (28% FTA). The vast majority of the participants who did not

finish the study failed to attend a visit and were then uncontactable, despite having multiple contact methods.

Acceptability and feasibility

The study interventions and procedures were completed with little complication. High rates of data completeness were achieved for all of the questionnaires and outcome measures assessed in the clinic. The biological samples (saliva, GCF and subgingival plaque) were collected without problems from all participants (where collection was possible i.e. not from the three participants who did not have enough healing time at the 3-month visit, following their periodontal therapy). However, the weekly smoking questionnaire had poor completion rates with only 30% of participants completing it at least 80% of the time, meaning no valid data could be derived from these.

Of those patients who failed to complete the study, most dropped out after the completion of the active periodontal therapy, prior to the review visits (4 weeks, 3 months and 6 months). This could have been because some participants placed little value in the review visits after receiving the active periodontal therapy; future trial designs could consider appropriately positioned incentives to reduce participant attrition (Brueton *et al.*, 2014). It is also possible that the burden of visits contributed to the participant attrition rate with participants having to attend six visits over six months. This number of visits is normal for patients undergoing a course of periodontal treatment (with review), but may have been too intense for those participants who were irregular dental attenders previously (i.e. those recruited from DEC and some PIC sites). This is supported by the differential retention rates observed between recruitment sources with PIC and DEC participants having considerably lower retention rates, 53% and 66% respectively. Future trial designs should consider whether the number and duration of the study visits can be reduced, and the setting of the research study changed, in order to minimise participant attrition.

Outcome measures

Descriptive statistics could be produced for the nine oral health outcome measures and five smoking outcome measures, as planned. The microbiological and inflammatory biomarker analysis were exploratory and for the purposes of the pilot trial analysis focused on the ability to collect the samples rather than the laboratory findings and meaning thereof.

Statistical significance testing was not conducted, in keeping with the pilot design of the trial, which was not powered to measure efficacy/effectiveness or to carry out hypothesis testing. However, point estimates with 95% confidence intervals have been presented for the outcome

measures. Overall, the oral health outcome measures showed improvement during the study, with broadly similar changes in both groups. For example: the mean PPD reduced by 0.7 mm (95% CI: 0.5-0.9) in the control group and by 0.8 mm (95% CI: 0.6-1.0) in the intervention group; the percentage of sites with severe disease (PPD ≥5 mm) reduced by 19% (95% CI: 14-24) in the control group and 22% (16-27) in the intervention group; and the patient reported oral health quality of life (OHQoL-UK) improved by 9 units (95% CI: 0-16) in both groups. There was no evidence of difference between the traditional and novel periodontal outcome measures.

The smoking outcome measures also showed improvement during the study. There appeared to be greater improvements in the intervention group, although this needs confirming in an appropriately powered definitive trial. For example, eCO reduced by 6 ppm (95% CI: 1-10) in the control group and 12 ppm (95% CI: 8-16) in the intervention group. A range of smoking abstinence measures were used; the RS6-eCO was 5% in the control group and 15% in the intervention group.

Key parameters for a future trial

A future trial would likely have co-primary outcome measures: a measure of smoking abstinence and one of periodontal health. The outcome measure estimates derived in this pilot trial can be used to inform sample size calculations for future definitive trials. The design of a future definitive trial should consider methods to address the e-cigarette use by the control group e.g. utilising a wait list control design, although this may have implications for the control group cessation rate.

A summary of the key findings for this pilot trial is presented in Table 3.44, which is based on methodological issues for feasibility studies as identified by Shanyinde *et al.* (2011).

Methodological issues	Findings	Evidence
1. Did the feasibility study allow a sample size calculation for the definitve study?	Retention rates estimated.	Target of 80 achieved at a rate of 5.3 participants/month. A retention rate of 73% was achieved at 6 months.
	Variability of outcome measures estimated.	See Table 3.34, Table 3.35, Table 3.36, Table 3.37 and Table 3.38.
	Sample size calculation for definitive trial was conducted.	Number of potential participants needing to be identified: 1162 Number needing to be randomised: 674
2. What factors influenced eligibility and what proportion of those approached were eligible?	A small number of those identified to the research team were ineligible. This because they had started using an e-cigarette or stopped smoking.	5 out of 119 potentially eligible participants were ineligible. For those attending the periodontal new patient clinic the main reason for ineligibility was being a non-smoker. We are not able to comment beyond this from the data collected in the study.
3. Was recruitment successful?	Yes, the required number of participants were recruited over 15 months.	Initially recruitment was slow. Once PICs and DEC started contributing the recruitment rate improved.

Methodological issues	Findings	Evidence
4. Did eligible participants consent?	Approximately a third of potentially eligible participants progressed to enter the study. The main reasons for not progressing were work or personal commitments, disinterest and failing to attend visits.	80 out of 114 eligible participants progressed to consenting and entering the study.
5. Were participants successfully randomised and did randomisation yield equality in groups?	Worked well.	40 participants were randomised to each group. A good balance of the majority of demographic variables was achieved. However, those in the control group appeared to have more severe periodontal disease and this may be need to be a stratification variable in the future definitive trial.
6. Were blinding procedures adequate?	This worked well.	As planned, the oral health outcome assessor was blinded.
7. Did participants adhere to the intervention?	The intervention group adhered well to the e-cigarette intervention. Several participants in the control group contravened instructions not to use an e-cigarette.	90% of the intervention group were using the e-cigarette at the quit date. 20% [95% CI: 11%-35%] of the control group used an e-cigarette at some point in the study.

Methodological issues	Findings	Evidence
8. Was the intervention acceptable to the participants?	The intervention was acceptable to the participants.	39 of 40 participants accepted the e-cigarette starter kit. 11 (28%, 95% CI: 16%-43%) participants chose to use non-recommended e-liquids. Over half [53%, 95% CI: 38%-67%] of the participants in the control group confirmed using the e-cigarette for the 6 months of the study. The participants interviewed provided positive feedback on the e-cigarette intervention (see chapter 5).
9. Was it possible to calculate intervention costs and duration?	Not formally assessed within this pilot trial but estimated costs provided.	E-cigarette starter kit cost: £38.97 (eTank starter kit = £14.40, additional e-liquid = £3.60, spare battery = £9.99, spare tank = £4.99, UK plug = £5.99). These costs are those incurred by the pilot trial and correct as of July 2016. Healthcare professional costs: Approximately a 10 minute tutorial was delivered with the e-cigarette starter kit. If a dentist delivered the tutorial this would cost £6.80 compared to £2.10 for a dental nurse (T Homer, personal communication, 6 August 2018). Total cost: £45.77 (dentist delivery)

Methodological issues	Findings	Evidence
10. Were outcome assessments completed?	There was good completion of outcome assessments in clinic. The weekly smoking questionanire was poorly completed by the participants.	See section 3.5.15. See section 3.5.7 and Table 3.24.
11. Were outcome measured those that were the most appropriate outcomes?	The outcome measures allowed assessment of periodontal health and smoking behaviour.	The traditional and novel measures of oral health allowed detailed assessment of oral health and oral health related quality of life. The smoking outcome measures allowed assessment of smoking reduction and abstinence.
12. Was retention to the study good?	Retention was acceptable.	Retention was similar to that predicted (73% versus 75%).
13. Were the logistics of running a multicentre trial assessed?	Not assessed within the pilot trial.	-
14. Did all components of the protocol work together?	No problems were identified.	There were no difficulties in following the protocol in order to recruit, randomise and deliver interventions to the participants.

Table 3.44 Summary of findings against methodological issues for feasibility studies.

*The methodological issues in this table are based on those discussed by Shanyinde *et al.* (2011).

3.6.2 ***Relationship to previous research***

Participant recruitment and retention

Previous research in this field has rarely provided in-depth descriptions of participant recruitment. There are only two comparable prospective studies (Preshaw *et al.*, 2005; Rosa *et al.*, 2011), as identified in a systematic review (Chambrone *et al.*, 2013). Rosa *et al.* (2011) screened 201 patients attending a smoking cessation clinic over a two-year period, finding 93 (46%) to be eligible, who were subsequently recruited to the study. Preshaw *et al.* (2005) recruited 49 patients from the clinics of a dental hospital, in a similar method to that used in the current study, but did not report the number of screened patients.

The 27% 6-month attrition rate of the current study is in keeping with these studies. Rosa *et al.* (2011) reported a 32% 6-month attrition rate and the study by Preshaw *et al.* (2005) reported a 41% twelve-month attrition rate [as reported in Nasry *et al.* (2006), 6-month data not reported].

Eligibility criteria

The current study had several medical conditions as exclusion criteria or as areas requiring further discussions. The information leaflet for the product we used in this study specified it not being suitable for pregnant or breastfeeding women, those who should avoid using tobacco or nicotine products for medical reasons and those with unstable heart conditions, severe hypertension or diabetes. However, as the product was regulated under the TPD and not as a medicinal product, we took a precautionary approach and applied those conditions detailed in the summary of product characteristics for the e-Voke (an e-cigarette that obtained a medicinal licence in 2015, but was never made commercially available) (Medicines and Healthcare products Regulatory Agency, 2015) and other forms of NRT e.g. Nicorette 15mg Inhaler (Medicines and Healthcare products Regulatory Agency, 2011). These 'special warnings and precautions', are more comprehensive but broadly similar to the instructions on the TPD product, and are based upon those developed for traditional NRT. They are included either because nicotine can affect the condition (e.g. nicotine can exacerbate oesophagitis, gastritis or peptic ulcers) or the condition can affect the clearance of nicotine, increasing adverse effects (e.g. severe renal impairment).

Other research has used less stringent eligibility criteria regarding medical conditions. For example, Hajek *et al.* (2015c) only excluded pregnant or breastfeeding patients; Bullen *et al.* (2013) excluded pregnant or breastfeeding patients, those who had a heart attack, stroke, or severe angina in the previous two weeks, and those with poorly controlled medical disorders;

and Caponnetto *et al.* (2013) excluded those with symptomatic cardiovascular disease, symptomatic respiratory disease, regular psychotropic medication use, current or past history of alcohol abuse, pregnancy or breastfeeding. The eligibility criteria (medical conditions) used in the current study, although stricter than previous research, did not appear to adversely affect eligibility rates (based on the limited data we have from the periodontal new patient clinic in which only one out of 391 patients was ineligible on medical grounds) and similar criteria could be used in future studies.

The minimum number of teeth required to be eligible for this study was reduced from 20 to 16 part way through the study (after seven months' recruitment). We found that, due to the severe nature of periodontal disease in some smokers, many of the potential participants had suffered from tooth loss and had less than 20 teeth. We reviewed the reason for using 20 teeth as a cut off and found this to be arbitrary. Comparing to previous research, Rosa *et al.* (2011) required 10 teeth whilst Preshaw *et al.* (2005) did not specify. We decided to revise our lower limit to 16 teeth which represents half of the dentition of a normal adult, giving a fair representation of the disease profile and enough teeth for the periodontal measures to be useful and for samples to be collected. Data were not available on the number of potential participants who were rejected on the original criteria (20 teeth). However, following the amendment, 11 participants (out of approximately 69 identified potentially eligible participants, 16%) had 16-19 teeth at baseline, showing the benefit in this eligibility criteria modification to the study recruitment.

Periodontal disease classification is worthy of further discussion given the recent changes (Caton *et al.*, 2018). Principally, the new classification system removes the terms chronic and aggressive, instead using a model based on staging and grading. There are four stages of severity and complexity of management, with extent being assessed as localised, generalised, or molar-incisor distribution. There are three grades for risk of progression/anticipated treatment response: slow, moderate and rapid. The field of periodontology is currently transitioning between the two systems and the current advice from the British Society of Periodontology (BSP) is 'for the time being it is recommended that clinicians continue to use the existing classification system' (The British Society of Periodontology, 2018). The periodontal disease eligibility criteria used in the pilot RCT anticipated recruiting individuals with chronic periodontitis but used a criterion based on having at least eight sites with a PPD ≥5 mm. A future study would be able to use the same criterion within the new classification system. Based on this our participants would be diagnosed as having periodontitis with stage III or IV and grade C (smokers of ≥10 cigarettes/day are classified as high risk) under the

new classification system (Tonetti *et al.*, 2018). A future definitive study would need to align with the classification system being used at the time.

Response to SCA intervention

The control group in the current study received SCA as part of usual care, achieving a 5% quit rate at both 4 weeks and 6 months (RS6-eCO). This is similar to the rates discussed in a Cochrane systematic review of brief advice interventions delivered by physicians, which concluded that the brief advice intervention could increase 6-month quit rates to 5% from the 3% unassisted rate (Stead *et al.*, 2013a). Another Cochrane systematic review focusing on smoking cessation within the dental setting concluded that quit rates could be increased to 7% (Carr and Ebbert, 2012).

The studies by Preshaw *et al.* (2005) and Rosa *et al.* (2011) reported particularly high 6-month quit rates, 29% and 33% respectively [Nasry *et al.* (2006) reported the 6-month quit rates for the study by Preshaw *et al.* (2005)]. These rates are considerably higher than that of the current study and there are two likely reasons for this discrepancy. Firstly, the interventions were more intensive than the current study. Preshaw *et al.* (2005) provided SCA but participants also had access to NRT and Zyban from the dental clinic. Rosa *et al.* (2011) also provided an intensive intervention which included four weekly 1-hour lectures, psychologist-assisted cognitive behavioural therapy, NRT or Zyban depending on clinical need and further smoking cessation counselling using motivational interviewing techniques at the four dental follow-up visits. Secondly, both studies only included smokers willing to quit, with Rosa *et al.* (2011) recruiting patients already choosing to attend a smoking cessation service and Preshaw *et al.* (2005) excluded 'contented smokers' who wished to continue smoking. The current study utilised a more pragmatic approach, including all smokers regardless of their intention to quit, therefore getting a real-world quit rate realistic to that achieved by these interventions in regular general dental practice.

Acceptability of e-cigarette intervention

Of the forty participants who were offered the e-cigarette starter kit in the current study, only one declined, giving a 98% (95% CI: 87%-100%) acceptance rate (this participant also declined any referral to the stop smoking services and did not make a quit attempt during the study period). This acceptance rate is in keeping with other RCTs (Bullen *et al.*, 2013; Caponnetto *et al.*, 2013; Adriaens *et al.*, 2014) who imply a 100% acceptance rate, although not explicitly stating this within their papers. A real-world e-cigarette acceptance rate is likely to be lower with one example reporting a 69% e-cigarette acceptance rate when smokers attended a stop-smoking service in London (Hajek *et al.*, 2015a). In a clinical trial scenario, a

high acceptability rate might be expected, with participants completing a thorough informed consent process prior to randomisation and any individuals not wanting to use an e-cigarette being less likely to engage with the study. Within clinical trials this unavoidable selection bias limits the external validity of results. However, in the current study, we tried to limit this by informing potential participants that the e-cigarette intervention simply involved having the offer of an e-cigarette starter kit, which they could decline and continue with usual care (SCA and option of referral to the stop smoking services).

Participants were advised to use the same brand of e-liquid as provided in the e-cigarette starter kit, as per manufacturer's instructions. The manufacturer's instruction manual states that only their brand of e-liquids should be used in the device and that vapour quality and satisfaction may vary if used other than recommended. Perhaps unsurprisingly, with the wide availability of e-liquids, 11 (28%) of the participants reported using a non-recommended brands of e-liquids during the study period. These participants made up the vast majority of the quitters in the intervention group, 83% of RS6-eCO and 75% of RS6-S. This suggests that these participants were more engaged with the intervention and experimenting with different products was an important aspect of the intervention, leading to success in quitting smoking.

Response to e-cigarette intervention

The recent Cochrane systematic review on e-cigarettes (Hartmann-Boyce *et al.*, 2016) included two studies which reported biochemically validated quit rates at four weeks of 23% and 14%, and at six months of 7.3% and 10-12% (depending on e-cigarette set up) (Bullen *et al.*, 2013; Caponnetto *et al.*, 2013). The intervention group in the current study, who received the e-cigarette starter kit, achieved similar if not higher biochemically validated (eCO) quit rates of 23% and 20% at four weeks and six months respectively (15% and 10% when applying the strict RS6-eCO and RS6-S respectively). Participant intention to quit varied considerably between the studies: Bullen *et al.* (2013) who only included those 'wanting to quit', Caponnetto *et al.* (2013) including only those 'not intending to quit' and the current study which did not have an intention to quit selection criterion. The higher quit rates seen in the current study could be due to changes over the five years since the original studies (Bullen *et al.*, 2013; Caponnetto *et al.*, 2013) including product improvements and increased social acceptability of e-cigarettes.

It was interesting to note that both of the RS6-eCO quitters in the control group used a self-purchased e-cigarette (against instructions) as part of their quit attempt.

Control group contamination

The current study had moderate contamination of the control group with 20% (95% CI: 11%-35%) of participants in the control group using an e-cigarette at some point in the study. The studies by Bullen *et al.* (2013) and Caponnetto *et al.* (2013) did not report on this, which has likely become more of an issue with the widespread availability and popularity of e-cigarettes in recent years. For example, Bullen *et al.* (2013) conducted their study in New Zealand between 2011 and 2013 where nicotine-containing e-cigarettes were illegal and population prevalence rates of use were low. Other studies (Caponnetto *et al.*, 2013; Adriaens *et al.*, 2014) utilised designs that did not have a non-e-cigarette control group. For example, Caponnetto *et al.* (2013) provided all participants with an e-cigarette but varied the nicotine content of the e-liquid, while Adriaens *et al.* (2014) used a wait list control design where participants in the control group were provided with an e-cigarette after two months.

The current study used a commitment form, similar to other studies (Hajek *et al.*, 2015c), in an attempt to minimise the use of non-allocated cessation products.

The moderate e-cigarette use by the control group in the current study illustrates a challenge for future research in this field. In studies where participants are allocated to non-e-cigarette options it is likely there is going to be considerable contamination, given the widespread popularity and availability of e-cigarettes. Completely inhibiting e-cigarette use by participants in the control group poses ethical dilemmas. For example, a participant may try the allocated (non-e-cigarette) intervention and be unsuccessful, but then decide they want to quit using an e-cigarette, and it would be unethical for researchers to stand in the way of a quit attempt. The relatively high reporting of non-compliance in the control group in this study is likely to be due to an open approach by researchers who encouraged honesty without consequences. Additionally participants were aware that salivary analysis was being undertaken, potentially increasing honesty in reporting smoking status.

Response to periodontal therapy

Conventional non-surgical periodontal therapy was provided in this study and mean PPD reductions of 0.7-0.8 mm were observed. This magnitude of reduction is in keeping with existing research (Heasman *et al.*, 2006). Studies with at least three months follow-up have shown a range of mean PPD reductions in smokers: 0.2 mm (Rosa *et al.*, 2011), 0.33 mm (Grossi *et al.*, 1997), 0.5 mm (Preshaw *et al.*, 2005), 0.65 mm (Pucher *et al.*, 1997), 1.02 mm (Ryder *et al.*, 1999), 1.23 mm (Palmer *et al.*, 1999), 1.35 mm (Tomasi and Wennstrom, 2004), 1.6 mm (Jin *et al.*, 2000) and 1.9 mm (Renvert *et al.*, 1998). Although it is hard to directly compare studies, due to differences in interventions and designs, it is clear that the clinical

response to the periodontal therapy delivered in the current study was broadly similar to that previously reported in the literature.

Periodontal response to e-cigarette use

The current study, being a pilot trial, was not powered to show a difference in outcome measures. However, the periodontal response to the non-surgical periodontal therapy appeared to be broadly similar, if not slightly better in the e-cigarette intervention group. As previously discussed (see section 1.4.6), there is an absence of definitive research on the clinical periodontal effects of e-cigarette use. However, there are a number of non-randomised clinical pilot studies (Franco *et al.*, 2016; Reuther *et al.*, 2016; Tatullo *et al.*, 2016; Wadia *et al.*, 2016; Javed *et al.*, 2017a; Al-Aali *et al.*, 2018) which all indicate improvement in oral health when tobacco smokers switched to vaping e-cigarettes, in keeping with the findings of the current study. A definitive study, powered to undertake this analysis is required and has recently been called for in a large national review (Stratton *et al.*, 2018).

The pilot study by Wadia *et al.* (2016) concluded that there was a significant increase in BOP at 2 weeks when smokers switched to vaping. As previously discussed, this study (Wadia *et al.*, 2016) has several flaws: inappropriate statistical testing for a pilot study, flawed power calculation, no control group and inappropriate interpretation (it is well documented that smokers have a short term increase in BOP when they quit, potentially accounting for the results of the study by Wadia *et al.* (2016)). Nevertheless, the results from the current study showed similar percentage BOP reductions in both groups indicating there was not a major clinically significant detrimental effect of the e-cigarette on BOP.

Participant weekly smoking questionnaire completion rates

The current study asked participants to complete a weekly smoking questionnaire, enquiring about their smoking habits over the previous seven days. The majority of participants (85%) opted for our default option which was a SMS text message with a link to the online survey. A small number (12%) requested the link sent via email, with 4% completing a paper version of the questionnaire. Although most participants (85%) completed at least one questionnaire entry, more regular completion rates were poor. Only 30% of participants completed the questionnaire at least 80% of the time, increasing to 41% for those 59 participants who completed the study. Completion peaked at quit date, dropped in the first 4 weeks, plateauing for the remainder of the study (see Figure 3.7). Completion rates were slightly lower in the control group.

The benefit of this data collection technique is the reduction in recall bias by collecting contemporaneous data. Participant diaries have often been used in research, often utilising a paper and pen format. However, as technology has developed, different mediums have been used to collect the data (Jones and Woolley, 2014). The range of weekly smoking questionnaire formats available in the current study allowed participants' preferences to be accommodated. The poor completion rates of the weekly smoking questionnaire by our participants was disappointing and worse than that reported by similar studies (Aigner *et al.*, 2016). Possible explanations for this include that this was one of several data collection methods in the study, rather than the only method used in some other studies which achieved higher completion rates.

The findings of the current study therefore highlight that this research data collection technique has poor completion rates in the study population and should be avoided in future research without considerable redesign e.g. use of incentives or less frequent questionnaires (once every 4 weeks).

Interestingly a number of the participants felt the weekly smoking questionnaire was acting as an intervention in itself. Below is an illustrative quote from one of the TDF interviews.

> It's [the weekly survey] made me aware, that, even though that you're not there, you're still there, in the background… Just lurking, you know, that you've still got the, like the, the long reach, support that you know, I've still got that connection, with the study. And you're not getting forgotten about. What you're doing, matters, because you want these, statistics… it does make you sit down and evaluate it and look at it at the wider picture if you like. (Female, 52 years, 15 cigs/day)

Adverse events

The current study reported no SAEs and 56 AEs which were mainly associated with the sequelae of severe periodontal disease e.g. toothache, dentine hypersensitivity, tooth loss and abscesses. Thirty-five percent of participants in the control group and 53% of participants in the intervention group reported an adverse event. This is in keeping with previous e-cigarette RCTs with Bullen *et al.* (2013) reporting approximately 45% of participants reporting an AE.

Direct comparison with previous periodontal research is difficult as adverse events have rarely been reported. For example, Rosa *et al.* (2011) and (Preshaw *et al.*, 2005) did not report adverse events in their papers. The Cochrane systematic review on e-cigarettes (Hartmann-

Boyce *et al.*, 2016) found that the most frequently reported AEs were mouth and throat irritation. This is in keeping with the current study, which also reported that a number of participants, exclusively in the intervention group, reported mouth ulceration or soreness of the intra-oral soft tissues. The number of these AEs was small (5 events in 5 participants) but the increased number occurring in the intervention group could be related to the e-cigarette intervention (other forms of orally-administered NRT have been associated with soreness and ulceration) or could be the result of the higher quit rate in the intervention group (smoking cessation is associated with soreness and ulceration).

3.6.3 ***Strengths and limitations***

Strengths

A strength of the current study is the broad and complementary nature of the mixed research methods utilised. The pilot trial focused on quantitative data collection with regards to smoking and periodontal/oral health whereas the broader feasibility study also utilised qualitative research methods (participant interviews) in order to gain a deeper understanding of the interventions and research processes (see chapters 4 and 5).

The feasibility study was well designed and complied with reporting guidelines. The CONSORT checklist for pilot and feasibility studies (Eldridge *et al.*, 2016) has been used, complying with 35 of 35 relevant checklist items which compares favourably to the previous research in this field which achieved scores of 5/28 to 12/29 (see section 3.2). Similarly, the interventions provided in this study were reported in detail using the TiDieR checklist, enhancing transparency and reproducibility.

As discussed earlier (see section 3.2), previous studies investigating oral health and e-cigarettes were generally poorly designed and hence this study is the first properly conducted pilot trial in this field. The findings from this study will allow for a well-designed and efficient definitive study in order to answer the research question.

Limitations

The contamination rate of the control group (using e-cigarettes, when asked not to) was an important finding of the current study. On the one hand, this is a limitation as it makes the interpretation of the results challenging, but on the other, it is an important feasibility outcome that will shape the design of a future definitive study.

The current study was conducted in a single specialist dental clinical research facility within a secondary care environment, where the chief investigator and principal investigator were based. This allowed for dedicated experienced research teams to conduct high quality research

but applicability to primary care may be reduced compared to a study conducted in a primary care environment. Future studies should consider this in their design.

The control group in the current study appeared to have more severe periodontal disease at baseline than the intervention group. Ideally, the groups should have balanced disease profiles and hence a future definitive study should stratify for periodontal disease severity.

This study used several measures of smoking abstinence, including the Russell Standard (West *et al.*, 2005b). The Russel Standard has six criteria of which this study fully complied with five. The sixth specifies that follow-up data should be collected blind to smokers' allocation, which was not completely possible in the current study. Periodontal/oral health outcome measures were collected by a blinded outcome assessor but the smoking outcome measures were collected by non-blinded members of the research team. This was mainly for practical reasons and resource limitations of a doctoral fellowship project. The reason West *et al.* (2005b) include this criterion is to avoid differential efforts being devoted to contacting subjects in different treatment groups and they recommend follow-up rates should be reported by group. The current study reported detailed follow-up rates by group and the findings show that equal numbers of participants (29 in each group) completed the study. Table 3.20 presents key parameters by randomisation group for those who were lost to follow-up compared to those who completed the study. Those participants lost to follow-up appeared to have higher eCO and FTND readings and more severe periodontal diseases, although probably not statistically significant. It is noteworthy that in the study by Bullen *et al.* (2013) the research assistants (and project co-ordinator) were not blinded. Caponnetto *et al.* (2013) did manage to achieve blinding as the e-cigarettes provided looked identical, with the pharmacy conducting randomisation and preparation.

A challenge with all e-cigarette research is the rapidly moving pace of the field, particularly with regards to product development and population use. It is common for e-cigarette devices used in research studies to become obsolete or discontinued throughout the duration of the study. In the current study we used a second generation tank design, the Vype eTank, which was still on the market at the close of the study (Waitrose, 2018), although not on the manufacturer's website (Vype, 2018). However, over the two years from choosing the product to the close of the study there has been considerable product development and this device is now largely superseded, for example, by the eTank Pro in the Vype product range. The rapid changes in popularity and usage of e-cigarettes also potentially makes the applicability of the findings challenging. For example, the eligibility criteria of the current study required participants not to have used an e-cigarette regularly within the last month. With ever

increasing uptake of e-cigarettes by smokers, this could potentially lead to decreases in the eligibility rates observed in the current study. However, the rapid rise in e-cigarette popularity appears to have plateaued over the last few years, indicating that the findings are likely to still be applicable. Nonetheless, in order for the findings of the current study to remain of optimum relevance, it is important that the definitive study is instigated rapidly.

3.6.4 *Implications for future research*

Recruitment

Participant recruitment to a future definitive study should utilise findings from the current study. A recruitment rate of five participants per month can be expected for a dental research centre such as the one used in this study. In order to achieve sufficient participant numbers it is likely that a future study would need to utilise a multi-centre and/or primary care approach. Future studies should be aware of the differences between recruitment sources with regards to the proportion of potential participants fully entering the study e.g. less than half of potential participants identified from primary care (PICs) converted to fully entering the study. However, higher rates might have been achieved if the study visits were carried out in primary care e.g. by a research team (research dental nurse and hygienist) visiting the practice on a regular session.

Eligibility criteria should follow the current pilot study by requiring 16 teeth (rather than 20) and not including willingness to quit in the criteria.

Study design

Future research should utilise a pragmatic study design, similar to the current study, which allowed inclusion of a broad range of participants and has wide applicability of the findings to general dental practice. The randomisation process should include stratification on periodontal disease severity in order to achieve balance between the groups.

Future research should consider appropriate designs to reduce or account for e-cigarette use by the non-e-cigarette control group. One option may be to utilise a staggered approach (i.e. a wait list control design) where all participants are offered an e-cigarette but at different time points, some at the start of the study and some after six months, in a similar approach to Adriaens *et al.* (2014) (participants were given e-cigarette at baseline or after eight weeks). Participants in the non-e-cigarette control group may be more likely to refrain from e-cigarette use if they know they are going to be provided one in the (near) future. This design would be good to address the research question about the potential effects of e-cigarettes on smokers' periodontal health. This is because the group not initially using the e-cigarette would likely

achieve a low quit rate, achieving a good comparison. However, this design would be suboptimal for comparing the efficacy of the interventions on smoking cessation outcome as the usual care intervention would likely be affected by this staggered design with some participants choosing to delay their quit attempt until they get the e-cigarette (in six months time).

Another option is to not have a non-e-cigarette group, instead both groups are provided with an e-cigarette, either with or without nicotine, in a similar design to previous studies (Caponnetto *et al.*, 2013). Again this design option has limitations, as it assesses the effect of nicotine in the e-cigarettes rather than the whole intervention (e.g. hand-to-mouth, vapour production, flavours) which limits its relevance and external validity. A pragmatic trial design could also be used, similar to the current study, evaluating the effect of offering an e-cigarette (rather the effect of using an e-cigarette). Framing the question in this way minimises the impact of e-cigarette use in the control group.

In the current study, participants were aware that the study was investigating e-cigarettes and some may have felt disappointed when they were allocated to the non-e-cigarette control group and therefore purchased their own e-cigarettes. It would be possible to redesign the participant information to include less focus on e-cigarettes, making it more broadly about smoking cessation, and possibly reducing the e-cigarette use by the control group. A clustered design approach in which a whole research centre or dental practice is allocated to the non-e-cigarette or e-cigarette group may further assist with this, although this would require a larger sample size (due to intra-centre correlation) and may not be acceptable to some centres.

The e-cigarette intervention delivered in this study was well received and future research could utilise a similar approach whereby participants are provided with a starter kit and expected to source their own supplies after the initial period. It is important to have a range of flavour choices, tobacco and non-tobacco.

Future studies should consider design features to enhance participant retention. In the current study, the most frequent time point for participants to drop out was during the review period, after completion of the active periodontal therapy. Future studies should consider incentives to enhance retention through these review visits. A recent Cochrane systematic review investigated strategies to improve retention in randomised trials, and although several trials investigated this in the context of questionnaire responses, very few evaluated ways to improve participant retention in a study (Brueton *et al.*, 2014). Monetary incentives were shown to be effective in increasing questionnaire responses and other strategies needed

further evaluation. Only one study investigated the effect on participant retention and found no difference when participants were provided with a certificate of appreciation and/or a lapel pins (Bowen *et al.*, 2000).

Consideration should also be given to reducing the burden of the study by reducing the number and frequency of the study visits. For example, follow up periodontal data could be collected at the 6-month visit rather than at both 3-month and 6-month visits. In the current study, the 3-month periodontal data could not be collected on all participants due to the proximity of their periodontal therapy completion. Furthermore, the 6-month time point corresponds with the time points for the smoking outcome measures (e.g. Russell Standards), unlike the 3-month time point. The periodontal outcome measures in the pilot trial had similar responses at both 3 months and 6 months, indicating little information would be lost by removing the 3-month visit or at least by reducing the data collection at this visit. In a future study design, it would be important to see the participant at the 3-month time point to provide SPT but the collection of research data is not necessary.

Outcome measures

Future studies should minimise the number of outcome measures collected in order to reduce participant burden. The current study had 16 outcome measures and these could be reduced in a future definitive study. A future study would likely have co-primary outcome measures: a measure of smoking abstinence and one of periodontal health. For the smoking outcome measures it would be important to collect self-reported use, eCO and possibly SC/SA in order to establish smoking abstinence. The FTND is a useful baseline measure of nicotine dependence, which could also be repeated at six months. The MPSS assesses withdrawal symptoms which is not directly relevant to this study and hence this assessment could be removed from the future definitive study. For the oral health outcome measures there should be no change to those collected in this study. The majority of the indices collected are required as part of usual care (PPD, MGI, PI, CAL, BOP) or derived from these measures (PISA, PESA). The CODS is an important measure to continue in a definitive study due to the potential drying effect of e-cigarette vapour. The OHQoL-UK questionnaire is an important patient reported outcome which should be continued in a future definitive study.

A set of core outcome measures for periodontal studies is under development using the Core Outcome Measures in Effectiveness Trials (COMET) methodology (Glenny *et al.*, 2012; Lamont *et al.*, 2017). The results are not yet published but email correspondence has identified that five core outcomes will be recommended: probing depths, quantified levels of gingivitis, quantified levels of plaque, quality of life and tooth loss (T Lamont, personal

communication, 21 August 2018). All of these were collected in the pilot trial and should also be collected a future definitive study.

The collection of subgingival plaque and GCF for microbiological and inflammatory biomarker analysis should be reviewed in the design of a future definitive study, potentially being removed. This will depend on the findings from the analysis of these samples from the current study and the aims of the definitive study.

Sample size

A future definitive study should base its sample size calculation on the findings of the current study. It is proposed that the definitive study should have co-primary outcomes as there are two important outcomes under investigation: smoking abstinence rates and periodontal health. A sample size calculation based upon the outcome of smoking abstinence, requires 337 participants per arm which is also large enough to cover the periodontal health outcome measures (e.g. PPD or percentage of diseased sites [PPD ≥5 mm]). The participant attrition rate and eligibility rates seen in the pilot trial can be taken into account to provide estimates for the definitive study design.

3.7 **Conclusions**

It was feasible to provide an e-cigarette intervention for smoking cessation, for patients with periodontitis, within the dental setting. The data suggested that the intervention may improve smoking quit rates and may have minimal positive effects on periodontal health at 6 months. The findings of this study will inform the design and sample size of a future definitive study.

Chapter 4 **Perceived influences on smoking behaviour and perceptions of dentist-delivered smoking cessation advice: A qualitative interview study.**

4.1 **Abstract**

Background

Smoking cessation advice (SCA) from the dental team is an important aspect of patient care. Previous research has focused on dental professionals' perceptions of providing SCA and has identified facilitators and barriers to providing SCA. However, there has been a limited amount of research focusing on patients' perceptions of receiving SCA in the dental context. This study aimed to explore the views of patients with periodontitis receiving dentist-delivered SCA.

Methods

Theory-based, one-to-one, semi-structured interviews were conducted with a purposive sample of 28 adults who smoked tobacco and had recently received SCA as part of a course of dentist-delivered periodontal therapy. Participants were sampled to reflect a range of ages and smoking behaviours. The interview was based on the 12 domains within the Theoretical Domain Framework (TDF) to explore perceived influences on smoking behaviour. Interviews also elicited participants' views on dentist-delivered SCA. Interview transcripts were analysed thematically.

Results

In regards to perceived influences on smoking behaviour, a broad and complex range of themes emerged, covering all 12 of the TDF domains. Seven more prominent TDF domains (main themes in brackets) emerged: (1) social influences (family and friends, social pressures); (2) social/professional role and identity (identity - secret smoking); (3) knowledge (experiences/perceptions of stop smoking medications); (4) environmental context and resources (social, home and workplace environment, resources for smoking, resentment towards authority); (5) emotions (stress management, pleasure of smoking and fear of quitting); (6) nature of the behaviour (habitual nature, link to other behaviours, smell); (7) beliefs about consequences (health).

With regards to views on dentist-delivered SCA, five main themes emerged: (1) opportunistic nature; (2) personal context and tangible prompts; (3) positive context of cessation attempt; (4) lack of previous support; and (5) differences by comparison with doctor-led SCA.

Conclusions

From the perspective of the patient, dentist-delivered SCA was supported and positively received. Future research should focus on intervention optimisation based on the themes identified.

4.2 **Introduction**

The provision of SCA is an important aspect of patient care. Dental professionals in the UK are advised, in several guidance documents, to provide SCA to all their patients who smoke (National Centre for Smoking Cessation and Training, 2012c; The National Institute for Health and Care Excellence, 2018). There are variations in how SCA can be delivered as previously discussed in chapter 1 (see section 1.3.2 and Table 1.1). A recent Cochrane systematic review and meta-analysis identified a number of relevant studies and concluded that SCA delivered in the dental setting can be an effective intervention (Carr and Ebbert, 2012).

A number of cross-sectional surveys have investigated patients' perceptions of SCA delivered by dental professionals. The surveys generally report a positive attitude to dentist-delivered SCA, with increasing positive attitudes over time. Earlier studies reported lower rates of patient acceptance of SCA, with a US study (Campbell *et al.*, 1999) reporting that 58.5% of dental patients believed dental offices should deliver SCA. Similarly, a large Australian survey found 61% of patients agreed that they would expect their dentist to discuss smoking with their patients (Rikard-Bell *et al.*, 2003). This survey (Rikard-Bell *et al.*, 2003) questioned the effectiveness of non-medical clinicians in providing SCA, on the basis that patients reported low confidence in their dentist's ability to assist them in quitting with less than a third reporting to make a quit attempt if advised to by their dentist. The authors called for more research into the acceptability and effectiveness of SCA, and suggested that dentists would be justified in resisting calls to provide SCA to their smoking patients due to the questionable efficacy (Rikard-Bell *et al.*, 2003). More recent surveys have found 'very positive' attitudes towards dentist-delivered SCA with percentages over 80% reported when similar questions were asked of dental patient populations in Ireland and India (Terrades *et al.*, 2009; Sood *et al.*, 2014). Terrades *et al*. (2009) also discussed the potential usefulness of highlighting the visible effects of smoking (e.g. tooth staining) but this was not investigated within their study.

These cross-sectional surveys are limited by their design in providing any detail or depth of understanding regarding patients' perceptions. A reasonable body of qualitative evidence exists for dental professionals' perceptions of, and barriers to, providing SCA in the dental setting (Lala *et al.*, 2017). However, there are no published qualitative studies investigating patients' perceptions of dentist-delivered SCA. Within medical settings some limited qualitative evidence does exists of patients' perceptions of SCA. For example, Butler *et al.*

(1998) conducted in-depth qualitative interviews with patients attending general medical practices in South Wales. This study controversially concluded that not all smokers should be provided with SCA and that doctors should tailor their approach to the type of patient using a patient-centred approach (i.e. focusing efforts on individuals showing interest in quitting). This was widely criticised at the time with subsequent correspondence advising that doctors continue to deliver evidence-based, brief interventions (e.g. the 4A's approach) to all smokers regardless of doctors' assessment of patient willingness to quit (Liu and Tang, 1998; Solberg and Kottle, 1998). They (Liu and Tang, 1998; Solberg and Kottle, 1998) also highlighted that physicians should avoid emphasising the 'advise' components of these interventions, as they can be seen as unhelpful prolonged attempts to convince and warn. The findings from the study conducted by Butler *et al.* (1998) may not be entirely relevant to the dental setting given the large differences in the clinical setting and patient experience. Additionally, the modern relevance of this study is questionable given that it was conducted over two decades ago with considerable societal changes since then and a greater range of smoking cessation interventions now available.

Qualitative research interviews can be conducted in a variety of techniques: un-structured, semi-structured and in-depth (DiCicco-Bloom and Crabtree, 2006). The Theory Domain Framework (TDF) provides an effective structure for semi-structured interviews on behaviour change (Michie *et al.*, 2005; Cane *et al.*, 2012). Basing interviews on the TDF ensures all theory-based predictors of behaviour and behaviour change are covered. The TDF was developed by an expert consensus group who reduced 40 theories of behaviour, with 128 theoretical constructs, to 12 domains. The TDF provides a framework for ascertaining influences on behaviour and mapping to existing theory.

In summary, evidence from quantitative studies indicates a positive attitude to dentist-delivered SCA but there is an absence of any qualitative research providing depth of understanding. The aim of this study was to explore patient perceptions on dentist-delivered SCA using theory-based, semi-structured interviews in order to inform future intervention development and optimisation.

4.3 **Method**

4.3.1 ***Design***

One-to-one semi-structured interviews were conducted using a pre-specified interview schedule based upon the TDF (Michie *et al.*, 2005; Cane *et al.*, 2012). The TDF consists of 12 domains which represent broad explanations for behaviour and behaviour change hypothesised by current theory. The 12 domains comprise: 'beliefs about capabilities', 'knowledge', 'social influences', 'environmental context and resources', 'motivation and goals', 'behavioural regulation', 'memory, attention and decision processes', 'emotions', 'social or professional role/identity' and 'skills'. Using the TDF ensures comprehensiveness and ability to connect data to specific relevant theories.

4.3.2 ***Participants***

A purposive sample of twenty-eight adults was recruited from a larger group of eighty participants taking part in a two-armed feasibility RCT (described in chapter 3). Potential participants were approached face-to-face at their baseline study visit. All those who were approached to participate in the interviews accepted the invitation. The detailed eligibility criteria have been previously described in chapter 3 (see section 3.4.2) but briefly include adults smokers, not currently using an e-cigarette, with severe chronic periodontal disease. The purposive sample were selected to reflect a range of ages, gender, smoking behaviour (number of cigarettes/day), nicotine dependence (FTND), eCO measurements and RCT group (control/intervention).

4.3.3 ***Interview protocol***

A interview schedule (see Appendix S) was developed based upon the 12 domains within the TDF (Michie *et al.*, 2005), ensuring broad coverage of the theories of behaviour change within the interview. The schedule was designed to explore perceived influences on smoking behaviour, views on dentist-delivered SCA, views on e-cigarettes (chapter 5) and feasibility aspects of the research process (chapter 5). 'Smoking' was explicitly defined at the start of each interview, differentiating it from e-cigarettes and vaping. Participants were initially asked to confirm the details of their current and previous smoking behaviour, including previous quit attempts. Open questions were asked in each of the theoretical domains in order to elicit responses about smoking behaviour. The interview protocol was developed collaboratively within the research team. During a TDF training workshop, delivered by experienced researchers in this field, the interview protocol was piloted on workshop participants and refined. Further piloting was conducted within the research team.

4.3.4 *Interview procedure*

Participants were interviewed in person within a research dental surgery at the Newcastle (Newcastle upon Tyne, UK) DCRF. An initial interview was conducted shortly after the SCA intervention (usually at visit 3 of the feasibility RCT) with a follow-up interview approximately six months later (usually at visit 6 of the feasibility RCT). The initial interviews were conducted between September 2016 and January 2018 with follow-up interviews between February 2017 and June 2018. The interviews were conducted by myself, Richard Holliday, a male research dentist conducting a PhD. No other staff members were present for the interviews. The researcher had appropriate training having completed a Masters in Clinical Research (general qualitative research training) and a training workshop (interviewing skills and conducting theory domain interviews). The researcher also had day-to-day support from an experienced health psychologist with experience of using interviews of this design. There was no relationship between the researcher and participants prior to study commencement. The researcher was providing dental care, including SCA, for the participants as part of the pilot RCT. As with all qualitative research there was potential for researcher bias and a reflexivity statement is provided in chapter 6 (see section 6.4.1). There were no conflicts of interests and the interview schedule included a statement reassuring participants that there are no right or wrong answers, answers would not influence future care and that the participant was the expert from which the research team was trying to learn. Participants were aware of the aims of the research study as detailed in the participant information sheet (see Appendix G); primarily to investigate if e-cigarettes can help smokers (who have periodontitis) stop smoking. The study was approved by a NHS Research Ethics Committee (REC reference: 16/NE/0219). All participants provided informed written consent (see Appendix H) for participation in the feasibility RCT which included the possibility of being invited for interview. A £10 gift voucher was provided after completing each interview.

4.3.5 *Analysis*

Interviews were audio-recorded, anonymised and transcribed verbatim by a professional transcriber (David Anderson of Fairway Business Services). Field notes were taken if required. Although the TDF provided the structure for the interview schedule, the domains were not used as an explicit framework for the analysis. Instead interview transcripts were analysed thematically by the researcher using the domains as an initial framework but with expansion possible after an initial review of transcript content. Coding was completed using Nvivo software (QSR International Pty Ltd. Version 11, Edition: Pro, 2015). The reliability of the coding was checked by a second researcher (Dr Suzanne McDonald). Data saturation was

assessed and confirmed using standard recommendations (Francis *et al.*, 2010). Interview transcripts were not returned to participants for comment/correction, although the second interview gave an opportunity for participants to reflect on themes identified from the first interview. This study adhered to the consolidated criteria for reporting qualitative research (COREQ) and a completed COREQ checklist is included (see Appendix T) (Tong *et al.*, 2007).

4.4 **Results**

4.4.1 ***Demographic data***

Twenty-eight participants (12 male) completed baseline interviews, which were conducted shortly after SCA intervention delivery (6 to 48 days after intervention [mean: 25 days]). Six participants were lost to follow up and 21 participants completed a follow-up interview. Equal numbers of participants were recruited from each RCT group (control/intervention). Further demographic characteristics of the sample are displayed in Table 4.1.

Interview participants were aged 25-60 years (mean age: 45 years). Participants were heavy smokers, all smoking at least 10 cigarettes per day (median number of cigarettes per day: 15; mean eCO: 21 ppm), with a moderate level of nicotine dependence (mean FTND: 5). The interview participants represented a wide range of employment statuses with almost equal numbers in professional, intermediate and routine/manual/unemployed categories. The baseline interviews lasted between 10 and 52 minutes (mean length: 25 minutes).

	Not interviewed (n=56)	Interviewed (n=28)		
		All participants (n=28)	Randomised groups	
			Control (n=14)	Intervention (n=14)
Gender [n (%)]				
Male	27 (52%)	12 (43%)	7 (50%)	5 (36%)
Female	25 (48%)	16 (57%)	7 (50%)	9 (64%)
Age (years)				
Min	19	25	25	27
Median (LQ-UQ)	43 (38-50)	45 (36-56)	47 (37-57)	45 (35-53)
Mean (SD)	44 (11)	45 (11)	49 (11)	44 (10)
Max	71	60	57	60
Ethnicity [n (%)]				
White (British, Irish, other White)	47 (90)	28 (100)	14 (100)	14 (100)
Asian or Asian British (Indian, Pakistani, Bangladeshi, other Asian)	5 (10)	0	0	0
Age started smoking (years)				
Min	10	12	12	12
Median (LQ-UQ)	16 (15-17)	15 (14-16)	15 (14-16)	15 (14-16)
Mean (SD)	16 (3)	16 (3)	15 (2)	16 (4)
Max	24	29	20	29

	Not interviewed (n=56)	Interviewed (n=28)		
		All participants (n=28)	Randomised groups	
			Control (n=14)	Intervention (n=14)
No. cigarettes per day				
Min	10	10	10	10
Median (LQ-UQ)	15 (11-20)	15 (15-24)	15 (14-30)	15 (14-21)
Mean (SD)	17 (6)	19 (8)	19 (8)	18 (8)
Max	30	40	30	40
FTND				
Min	1	1	1	2
Median (LQ-UQ)	5 (3-6)	5 (3-8)	5 (3-8)	5 (4-6)
Mean (SD)	5 (2)	5 (2)	5 (3)	5 (2)
Max	9	9	9	9
eCO (ppm)				
Min	2	1	1	8
Median (LQ-UQ)	20 (12-28)	20 (11-28)	20 (11-27)	22 (13-28)
Mean (SD)	21 (12)	21 (11)	20 (12)	21 (10)
Max	55	49	49	40

	Not interviewed (n=56)	Interviewed (n=28)		
		All participants (n=28)	Randomised groups	
			Control (n=14)	Intervention (n=14)
Employment status [n (%)]				
Working in a routine or manual occupation	15 (29%)	6 (21%)	3 (21%)	3 (21%)
Working in an intermediate occupation	13 (25%)	9 (32%)	4 (29%)	5 (36%)
Working in a managerial or professional occupation	9 (17%)	9 (32%)	4 (29%)	5 (36%)
Unemployed/not working for a year or more	6 (12%)	2 (7%)	1 (7%)	1 (8%)
Full time student	1 (2%)	0	0	0
Retired	5 (10%)	0	0	0
Sick/Disabled/Unable to return to work	2 (4%)	1 (4%)	1 (4%)	0
Home carer (unpaid)	1 (2%)	1 (4%)	1 (4%)	0
None of these	0	0	0	0

Table 4.1 Demographic data of interviewed participants with comparison by intervention group and against those not interviewed.

4.4.2 *Overview of themes*

Smokers with periodontitis, attending the dentist for a course of periodontal therapy, have a broad and complex range of influences affecting their smoking behaviour and views about quit attempts. The following results section is organised into two broad areas: (1) views on influences on smoking behaviour and (2) views on dentist-delivered SCA.

Regarding influences on smoking behaviour, the interview data were coded within all 12 TDF domains, although seven of the domains were more prominent. These TDF domains (main themes in brackets) were: (1) social influences (family and friends, social pressures); (2) social/professional role and identity (identity - secret smoking); (3) knowledge (experiences/perceptions of stop smoking medications); (4) environmental context and resources (social, home and workplace environment, resources for smoking, resentment towards authority); (5) emotions (stress management, pleasure of smoking and fear of quitting); (6) nature of the behaviour (habitual nature, link to other behaviours, smell); (7) beliefs about consequences (health).

When specifically considering the dentist-delivered SCA five main themes emerged: (1) opportunistic nature; (2) personal context and tangible prompts; (3) positive context of quit attempt; (4) lack of previous support; and (5) differences by comparison with doctor-led SCA. Figure 4.1 details all the themes and sub-themes.

The following sections described the seven TDF domains and related themes regarding smoking behaviour followed by the five themes relating to dentist-delivered SCA. Direct quotes are provided and individual participant characteristics (gender, age, average number of cigarettes per day) are shown in brackets following each quote. Supplementary participant quotes are provided in Appendix U.

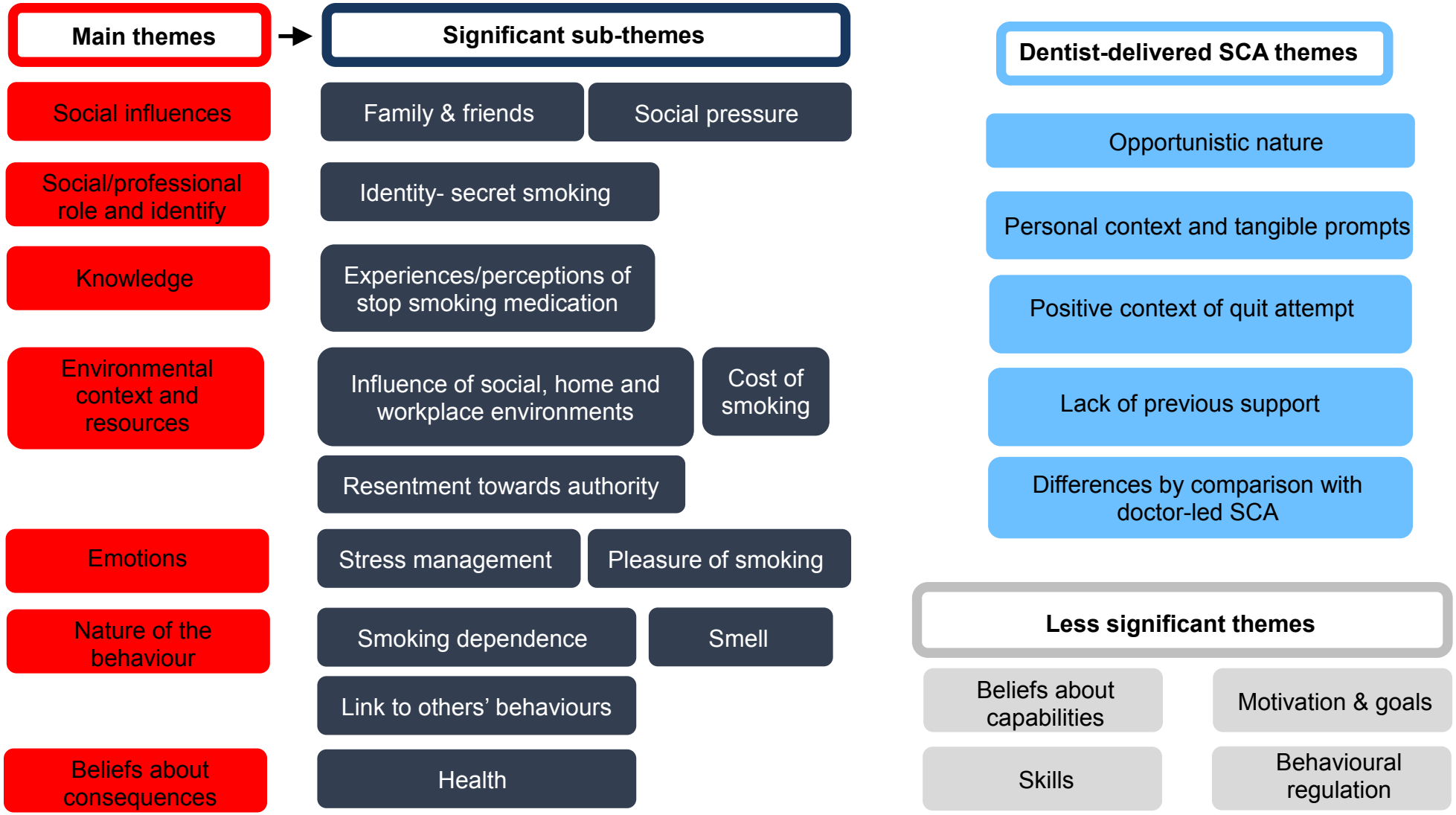

Figure 4.1 Coding tree

4.4.3 *Theory-based influences on smoking behaviour*

Social influences

The influence of family members and friends

A persistent theme that emerged from that data was that participants felt their smoking behaviour or quit attempt were strongly influenced by social factors. Often this was at an inter-personal level with participants perceiving that family members or friends influenced their smoking behaviour or quit attempts.

> Supportive [family]. Very much so… my other half [wife], she's an ex-smoker… her view is, "If you want to smoke, it's up to you. I don't mind, but if by not smoking, you're going to be around longer, then I'd rather you were around longer." That's her, quite grounded view of it. (Male, 56 years, 20 cigs/day)

This quote illustrates the supportive influence (social support) of a close family member on a quit attempt. The pressure exerted by the family member is indirect and not overpowering, perhaps due to her status as an ex-smoker. The participant appears to respect her view by referring to it as 'grounded'.

Other family members can also offer support, particularly young family members. The study participants were usually at least middle-aged and many reported that their children or grandchildren had a positive influence on their quit attempt.

> …me (my) son's just so positive, he doesn't smoke and we're (I'm) getting the proper Mam (mum) pep talk. So that's really good. (Female, 58 years, 15 cigs/day)

Younger family members are more likely to be non-smokers, as the above quote illustrates, and were often encouraging their older relatives (study participants) to quit smoking. Social acquaintances and friends also imparted influence.

> Really encouraging [friends]. So much, to the fact that, I think I told you, I was away this weekend, been across to Spain, and me pal's [friend] done exactly the same [quit smoking with e-cigarette]. (Male, 58 years, 15 cigs/day)

This quote illustrates the positive influence (on quitting) of a friend and demonstrates an example of collaborative behaviour. However, when participants had friends who were smokers they often found this to be a negative influence (on quitting).

> …I have avoided people who smoke. Because a lot of me [my] friends do smoke so I haven't been visiting them. 'Cos I thought the temptation's still early days at the moment. (Female, 45 years, 10 cigs/day)

In the early stages of a quit attempt participants often tried to avoid temptation, especially from friends, as illustrated in this quote. Participants reported avoiding situations or individuals that they perceived to have a negative influence on their quit attempt.

Social pressure

Beyond personal social influences, participants also perceived a strong influence of wider societal factors on their smoking behaviour. They had a strong sense that as smokers they were part of a minority.

> There's not a lot of people around me [that smoke], I don't think I even have any family that smoke anymore… Everyone has, who did smoke, which isn't many, has stopped (Male, 38 years, 10 cigs/day)

> It's not as noticeable as what it used to be [smoking]. It's gone down dramatically, the smoking. (Female, 57 years, 20 cigs/day)

These quotes demonstrate that participants had an awareness that smoking prevalence had steadily declined. This social comparison was both within their personal social circles (first

quote) and also at a wider population level (second quote). Beyond the sense that they were part of a minority they also felt strong negative societal pressures against smoking.

> There's no doubt that in the current climate where smoking isn't socially acceptable, that it's not a question of being forced to go outside to have a cigarette, because you'd feel very uncomfortable having a cigarette in somewhere with everybody else. (Male, 56 years, 20 cigs/day)

Participants reported being aware of injunctive norms (smoking was not welcome or socially acceptable), as illustrated in the above quote. In this case, the participant talks about feeling uncomfortable and this affecting his smoking behaviour. Similarly, other participants spoke of feeling 'embarrassed' to smoke in public. The age of the participant, in this case, is also important, as smoking was socially acceptable and a social norm for a large proportion of his life. In other cases this feeling went beyond feeling uncomfortable.

> It was different when you could smoke in pubs and it's not a social thing now I don't think it is… But now it's something that I don't want it to be [smoker]. (Male, 38 years, 10 cigs/day)

The societal pressures felt by this participant make them want to disassociate from being a smoker. The environmental context of the 'pub' is influential to many participants and this is explored in a later in this section. Participants often felt there was a poor physical image associated with a person smoking.

> I think is looks horrible. I think it looks awful when you see somebody walking down the street with a tab in their mouth. (Female, 49 years, 20 cigs/day)

As in this quote, participants often considered that smoking had a negative impact on appearance and was 'unattractive'. Some participants reflected that this influenced their own perceptions and potentially their smoking behaviour.

> …because society's changed, I think smoking now is not as acceptable anywhere, as it used [to be], I mean at one time you could have a cigarette in a restaurant, you can't now, it's not acc-, it's just not acceptable. So, and I want to be accepted. I don't want to be the one that's not accepted. I don't want to be the one that's not cool anymore. You know what I mean? I want to like, be cool. (Female, 52 years, 15 cigs/day)

This quote highlights many of the themes identified within this section. Societal changes are noted by the participant, leading to a perception that smoking is not acceptable or 'cool' (injunctive norms) and a desire to quit smoking in order to conform to societal norms.

Social/professional role and identity

Identity - secret smoking

Following on from the previous domain/theme (social influences/social pressure) some of the interview participants reported trying to hide their smoking behaviour and identified themselves as 'secret smokers'.

> …there's quite a few of my friends, don't know I smoke… I would go and sneak and have a cigarette somewhere… I don't know for me it was sort of a hidden type of thing, it was, as I say, I wouldn't go out and smoke, especially like at work. I don't think anybody at work knows I do smoke. (Female, 47 years, 10 cigs/day)

This quote highlights a participant who is trying to hide her smoking behaviour, identifying it as hidden or secret. This is particularly notable in public environments such as the workplace. This influence of the workplace is explored later in this section. For other participants, smoking was an important aspect of their identity.

> I like, old motorbikes, I like old unusual cars, I like old strong beers and stuff. It's almost as though, puffing on a roll up is, almost part of that… it's [smoking] become more of a hobby, one of my life choices is through motorcycling. 30 odd years I've ridden old Harley Davidsons everywhere. (Male, 56 years, 20 cigs/day)

This quote illustrates that smoking still has perceived value or is consistent with identity or behaviour in some groups in society. The participant felt smoking (rolled tobacco) was an important aspect of group identity (motorcycling culture) and this affected his smoking behaviour, making him less likely to make a quit attempt.

Knowledge

Experiences/perceptions of stop smoking medications

It was clear that many of the interview participants had made several previous quit attempts. They had extensive experience of using smoking cessation medications and/or services. Perceptions towards stop smoking medications were largely negative.

> And I've tried the patches… I stopped smoking for five weeks, but I was on the patches for four weeks of that. [Interviewer: OK. And how did you find them?] Terrible. Absolutely terrible. (Female, 58 years, 15 cigs/day)

This quote illustrates negative perceptions towards nicotine patches based upon the participant's personal experiences. Others developed opinions on stop smoking medications using feedback from other people.

> Well, apparently, the tablets are supposed to be quite good, but again they're, and they're supposed to give you, a lot of bad side effects I think... like dreams and sort of, so I was like, oh, not, something that I didn't want to ever try. (Female, 35 years, 10 cigs/day)

> [talking about Champix] I don't know how I feel about, almost brainwashing yourself… Yes, you're tricking your taste, but it's your mind that needs to be behind it. 'Cos you're still going to have the urge for the cigarette... and it's almost like you're fighting each other. Your mind's fighting your physical addiction. (Female, 37 years, 30 cigs/day)

Perceived side effects of stop smoking medications were mentioned by some participants, as in this case. Interviewees often cited side effects as a reason to justify not using the

medications in a quit attempt. Some participants felt uncomfortable with the lack of control and perceived 'brainwashing' traits of some of these medications. However, not all participants had negative experiences and perceptions.

> Well, the Champix one, that really really works. But, it just made me, an emotional wreck. I mean, normally things that I could deal with, I mean there was one lady, was moaning about there wasn't enough jam in her doughnut, and I was sort of like, "Well, I didn't make the bloody doughnut"… I just found I wasn't able to tolerate things. So I just, but I think I probably would consider it again… Because it really does work. You like, put a cigarette in your mouth and you're like, "I just don't want it". It's quite clever… Me Mum's done marvellous on it. (Female, 49 years, 15 cigs/day)

In this quote, although the participant experienced some negative side effects from the medication these appear to be outweighed by the positive effects experienced by the participant and her mother.

Environmental context and resources

The influence of social, home, and workplace environments

Participants reported that different environments had an influence on their smoking behaviour.

> …the clubhouse at the caravan. Yeah, there are sort of several areas where you can go and have a cigarette and there's always someone saying "Are you going to come out and have a cigarette?" (Female, 47 years, 15 cigs/day)

Social environments, especially those involving alcohol were often one of the hardest for participants to refrain from smoking in, as illustrated in the above quote. The link with alcohol is powerful and explored later in this section. The effect of smoke-free legislation was mentioned by several participants.

> I mean certainly nowadays when, if you happen to be down the pub and you want to have a cigarette, you have to go outside... so, I suppose that time that you spend outside, you could spend it inside, socially interacting, although the converse is also true, 'cos a lot of my friends like to stand outside anyway so... (Male, 47 years, 15 cigs/day)

> …it's all gone [social aspects of smoking] because the pubs have all stopped it [allowing smoking inside] so you feel like a pariah stood outside smoking (Male, 59 years, 30 cigs/day)

These quotes demonstrate how smoke-free legislation has changed behaviour in pubs in the UK, with differing experiences between the two participants. In the first quote the participant feels they have to smoke to be part of the social group that stands outside. Conversely, in the second quote the participant feels alienation and stigmatisation by having to stand outside. In some cases the social environment can also extend into the home environment.

> …'cos people come [to the house] and they all smoke… So I'm going to ban it after Christmas from me [my] house. [laughs]… I need a smokers' hut for me [my] back garden. (Female, 43 years, 20 cigs/day)

In this case the interviewee's friends were smoking in her house. She was aware of how this was negatively impacting her quit attempt and she was planning to challenge this in the near future. The influence of the workplace environment was perceived to be strong and to exert a negative impact on quitting attempts or success.

> When I'm at work I smoke quite a bit… So, that has been tough. (Female, 31 years, 30 cigs/day)

The workplace can be a tough environment during a quit attempt, as in the above quote, with people often finding it a setting in which they smoke a lot. For others, the challenge of this environment was the availability of tobacco from colleagues or as a coping mechanism for stress. The social interactions associated with smoking in the workplace also place pressures on a quit attempt.

> …there's a few smokers and you get to find out the gossip. Or who's twisting [complaining] about who. (Female, 40 years, 25 cigs/day)

Similarly to the earlier participant who feared missing out on social interactions in the smokers-area outside of the pub, this participant describes a comparable situation in the workplace. Another participant felt that the smokers' area was an important decision-making space.

> I say tongue-in-cheek really, we always laugh at work because… More decisions are made and you find out far more there [outside smoking area]. I'll sit in a meeting for hours, and we'll argue and debate, [then we'll] go out for a cigarette, someone will be there, 'So, we're going to do this, this and this...', 'Yeah.' (Male, 56 years, 20 cigs/day)

This office-based worker suggests that the outside smoking area is important for work-based relations both in terms of finding out information and making decisions. The participant introduces the comment by suggesting it might not be totally true (tongue-in-cheek) but then states that it is often acknowledged by co-workers which implies there is some reality to the statement. However, the negative influence of the workplace was not consistent and some reported that it had a positive influence on their smoking behaviour.

> Yeah. Work is quite formal so, I wouldn't even dream of smoking at work. Even, staff parties or whatever... (Female, 47 years, 10 cigs/day)

Only a small number of participants reported reduced smoking in the workplace. It was usually those with more professional or managerial roles and, as illustrated in the quote above, this was usually due to the perceived negative image associated with smoking.

Cost of smoking

Another prominent theme in interviews was the cost of purchasing tobacco products. Smoking was described as expensive, and participants drew comparisons with other goods or services that money could be spent on instead.

> Ridiculous amounts [spent on cigarettes]. That's the crazy thing. I'll see, I don't know, make-up, for example, I'll look for what's on offer. It's like a tenner, I'll be like [cautious], however I have no qualms what-so-ever in handing over £20 for 40 cigarettes. And that is crazy. Like, over a month it's like 200 odd pounds. So that is a significant amount, that's like what, half of a mortgage payment? If not, slightly more? But for some reason you don't think about anything about handing it over. (Female, 37 years, 30 cigs/day)

These participants, as illustrated in the above quote, were very aware of the significant proportion of their income they were spending on tobacco smoking. However, other interviewees felt unaffected by the financial costs of smoking.

> It's never been an issue… I'm not boasting, but... It's never been an issue with me… I would imagine it will be with quite a lot of people because it can be a bloody expensive exercise. (Male, 58 years, 15 cigs/day)

> …it's not expensive what I buy, buy cheap pouch tobacco, 50 grams I only pay £9 for it, which is cheap but, it lasts me two weeks you know. (Male, 27 years, 15 cigs/day)

These quotes illustrate that participants felt unaffected by the financial cost of smoking either due to their sufficient income (first quote) or, more often, due to access to cheap tobacco (second quote).

Resentment towards authority

A theme strongly voiced in a small number of interviews was resentment towards authority regarding smoking behaviour. This was usually targeted toward tobacco control polices and often focused around cost and taxes.

> ...the government shouldn't sell cigarettes, full stop. And then, they would save fortunes in dental healthcare and they would save fortunes in healthcare. 'Cos they wouldn't have all of this [these] problems. [I] Don't know why they don't just stop selling them, I mean they're making them so bad for you, why sell them in the first place? 'Cos they make too much money off them, that's why… But I mean, you think about even the country, I mean, how much money the governm- [government], the NHS would save, with smoking-related diseases. Absolute millions. (Female, 52 years, 15 cigs/day)

This participant gives a broad account of the reasons why smoking is bad for the healthcare system but cynically feels the government continues to allow the sales of cigarettes for financial reasons. The participant's use of language in reference to the government is noteworthy. They seem to imply that the government is the manufacturer of cigarettes and that they make them harmful on purpose, showing a deep resentment towards them.

Emotions

Stress management

Participants perceived a wide range of emotional influences on their smoking behaviour. Many associated increased smoking with stress and perceived stress as a barrier for unsuccessful quit attempts.

> …it's only really if there's like a stressful sort of situation going on and I think at the moment I'm in a good place at work that I haven't really had that much stress, lately, so that's probably why I'm in a better, frame of mind to sort of think about you know, stopping altogether. (Male, 45 years, 15 cigs/day)

This example highlights how participants linked smoking as a coping mechanism for stress. In this case, they felt the recent reduction in stress was beneficial for their quit attempt. Similarly

to stress, other participants cited major 'life events' as influencing factors on their smoking behaviour.

> ...three or four year ago, me mam [mother] died. So the first thing I done [did] was went and, went, after I'd come from the hospital...'cos we were there when she died, went straight to the shop, bought a lighter, bought a packet of cigarettes, so... (Female, 49 years, 15 cigs/day)

Several different types of 'life events' were cited as major influences on smoking behaviour or reasons for previous relapse such as relationship issues, moving house or bereavement, as in this case. These life events were usually negative or stressful events but one participant also had a positive 'life event' negatively impacting on their quit attempt.

> Yeah, got it [new job], yeah, I was happy about that, found out last night… I ended up having a cigarette because of it like (Male, 27 years, 15 cigs/day)

This participant celebrated getting a new job by having a cigarette, despite a recent period of abstinence. He used the cigarette as a reward following finding out the good news.

Pleasure of smoking

The pleasurable aspects of smoking emerged as a prominent theme in some interviews.

> But, it's a funny thing because, I don't mind smoking, I just know the damage it's doing to us [me]. You know like, I've never not enjoyed [smoking] (Female, 58 years, 15 cigs/days)

This participant has an internal struggle; she is well aware of the harms and negative aspects of smoking but enjoyed it and found it pleasurable.

Fear of quitting

A small number of participants articulated a 'fear' of stopping smoking.

> I think it's a fear, of hearing everybody going through such a horrific time, never fully getting over it, thinking oh, you hear about people 15, 20 years later, saying, "Oh, do you know, I could just do with a cigarette". And it's almost like torturing yourself, you're wanting something so much, but you can't have it. (Female, 37 years, 30 cigs/day)

In this quote, the participant is articulating a fear associated with a quit attempt. She describes nicotine withdrawal symptoms and craving for a cigarette.

Nature of the behaviour

Smoking dependence

The addictive and habitual nature of smoking was a major theme that emerged from the interview data.

> But, when you say how many do you smoke in a day, I don't actually stop, I wake up during the night [to smoke]... yeah, and I think, I'm not entirely sure, but it's a habit born out of addiction. But I've been doing that for years. I'm a lot better now than what I used to be... for example, last night, I went to bed at about half ten, and I was up just after midnight. Then I got up at three, and then I was up at about half four. But I literally, I go back to sleep straight away… It's almost like the urge to smoke is so subconscious I can't fully settle, it's strange… I don't know, I actually think it's a habit now. (Female, 37 years, 30 cigs/days)

This participant is demonstrating powerful nicotine dependence, having to break her sleep every two hours for a cigarette. Beyond the pharmacological dependence the participant feels her behaviour has now developed into a habit or routine.

Link to other behaviours

The participants' smoking behaviour was often linked to other behaviours/habits such as drinking coffee, tea or alcohol.

> I'll have a coffee and a tab [cigarette], a coffee and a cigarette. A cup and a tab [cigarette]. (Female, 58 years, 15 cigs/day)

In this quote the participant is revealing how intimately her smoking behaviour is linked to coffee drinking. It was very common for participants to describe the intimate relationship between smoking and drinking coffee or tea, almost as if they are the same behaviour. There was also a strong link to alcohol.

> I don't want to go out drinking anytime soon, 'cos I think that's the biggest pitfall for it. (Male, 27 years, 15 cigs/day)

As in this case, many participants were aware of social situations involving alcohol as being high risk for relapse during a quit attempt. Many tried to avoid these situations in the early stages of a quit attempt.

Smell

The smell associated with smoking emerged as a strong theme from the data. Many participants were acutely aware of the smells associated with smoking and presented strong views on this.

> I think the smell as well… You know, the amount of, sort of deodorant and the amount of perfume, the amount of, mints and mouthwash that I was using because actually I didn't like the smell of it, or the way it made my clothes and myself smell. So I think that's an advantage that I've seen already [of quitting], that I don't, you know, I'm not using as much mouthwash or anything. (Female, 47 years, 10 cigs/day)

This quote illustrates the awareness and self-consciousness of some participants about their smoking habit. This participant had developed a routine to mask the smell and was using the reduction in this as positive reinforcement during the current quit attempt.

Beliefs about consequences

Health

The majority of the participants had perceptions about the consequences of their smoking behaviour, with most of this centred on health concerns.

> And health wise, probably health wise is the main thing really. I've got a fear, and probably getting to the age now, the fear's going to kick in a bit more… I've got a fear of dying… Terrible fear. (Male, 60 years, 15 cigs/day)

Many participant were very concerned about the health damage caused by smoking, as in this quote. However, there were a wide spectrum of views with others less concerned.

> …I look at how old I am, you see, and sometimes I say to myself, "I ain't bothered if I live another 10 years. I really couldn't give a toss". And that's the thing in the head. You see. Doesn't bother us, because there's something better on the other side you know. (Male, 59 years, 30 cigs/day)

This participant articulates a view of having few concerns about their health, perhaps due to their beliefs. This viewpoint was unique amongst the participants interviewed. Some participants articulated health concerns in relation to quitting smoking.

> I'm just sort of like thinking… you know like smoking and stopping smoking is just like opening a Pandora's box. Do you know what I mean? (Female, 58 years, 15 cigs/day)

This participant was worried about the unknown and about making changes to a long-standing routine. Others spoke about behavioural changes such as 'not being a very nice person' or about weight concerns, particularly the fear of weight gain following quitting.

4.4.4 ***Dentist-delivered smoking cessation advice findings***

The following section presents findings with regards to the dentist-delivered SCA. Five themes are described with illustrating quotes.

Opportunistic nature

The opportunistic nature of the dentist-delivered SCA developed as a theme from the data. Several participants commented on the SCA being unexpected at the dental visit.

> Just coming in here, like last week, as somebody just offering you an olive branch, that hope, to think, whereas before I was just going on, and "I'll get round to it [quitting] one day". (Female, 58 years, 15 cigs/day)

This quote illustrates the opportunistic nature of the SCA and how it was viewed positively by the participant as an 'olive branch'. The SCA was often linked to the discussions about periodontitis, which also appeared to strongly impact several participants.

> And so it's sort of been like a slap in the face sort of thing, like, "Oh wow, I didn't realise it was doing that much damage". (Female, 29 years, 10 cigs/day)

Connecting the SCA to the periodontitis appeared to have had a powerful effect for several participants, as in this case. Others described similar reactions using phrases such as 'it hit me like a brick'. Several participants reflected on the dentist-delivered SCA being a significant moment in their journey to quitting.

> I was going to, I had planned on stopping anyway because of, moving house and wanting to stop, but I think sort of the gum disease, sort of, that was the final sort of, made the final decision. (Female, 47 years, 10 cigs/day)

As in many cases, this participant had existing intentions to quit smoking but the dentist-delivered SCA appears to be a major influencing factor along this journey.

Personal context and tangible prompts

Oral health considerations were commonly referred to as reasons for quitting with participants being very concerned about appearance and tooth loss. All the participants in this study had periodontitis and they often referred to the consequences of periodontitis as a motivation for their quit attempt.

> I had it in me [my] head, once I'd found out, about me [my] bones and me [my] gums and that, that I wanted to stop… It's given us that extra push really. (Male, 36 years, 15 cigs/day)

As in the previous section, this quote illustrates the perceived influence of dental considerations on the participants' quit attempt. The personal context of adverse effects seemed to be an important consideration.

> I know, the problems I've had with my front teeth. And that appears to be linked to smoking, because I started smoking again when issues started to happen and I think my personal appearance and my personal, sort of, feeling towards my teeth are more important and that's why I needed to stop smoking as well… I know, on some packets of cigarettes, there's some photographs and, it still doesn't put you off, but I think when it happens to you, then it's personal (Female, 47 years, 10 cigs/day)

In this quote, the participant chiefly talks about their aesthetic concerns related to the periodontitis and how this is having a strong personal effect on her, much more so than the health warning images she has seen on cigarette packets. Several of the participants referred to a form of visual prompt that influenced them.

> ...so, when I seen how bad the back of my teeth are, I don't know how I didn't notice that but, when I did notice that, [laughs] that was a click... (Male, 27 years, 15 cigs/day)

> I thought me teeth looked disgusting on that X-Ray… 'cos they were coming out of the bone weren't they? (Female, 57 years, 20 cigs/day)

These quotes illustrate that the visual appearance of their teeth (e.g. tooth staining, drifting, tooth loss) or the x-ray appearance were influential aspects of the dentist-delivered SCA.

Positive context of quit attempt

In this study, the SCA was delivered as part of a course of periodontal therapy. Several of the participants focused their quit attempt on positive aspects associated with reducing the ongoing damage to their periodontal health or with the outcomes of the periodontal therapy e.g. improved outcomes.

> I know I'm having treatment but at the end of the treatment as long as I'm not smoking, there is going to be lots of improvement. Rather than carry on smoking and having the treatment it's... it's sort of outweighing itself really, there's not much point. (Female, 45 years, 10 cigs/day)

This participant is framing her quit attempt in a positive context alongside their periodontal treatment. Likewise, some participants reflected on the positive early outcomes of their periodontal therapy.

> I'm really pleased with, the outcome of that cleaning of my teeth and I really don't want to, spoil it… Yeah, I'm really so pleased, they feel, lovely. Mm-hmm. (Female, 49 years, 20 cigs/day)

This quote highlights how the early outcomes of periodontal therapy, such as cleaner teeth, were noted by participants and used as a motivation to quit or remain abstinent from smoking.

Lack of previous support

There were also some negative perceptions about previous dental care in relation to smoking cessation particularly around a lack of previous advice.

> …my normal dentist never ever told me it was that [smoking was a risk factor for periodontitis]. It was just some infection I got… I never, I mean, yes, I knew it probably would cause some kind of damage to my gums at

> some point, but, because I've never been told that, it's never kind of, stuck there. I mean, if I had been told that years ago, when I first started, then probably it would have been a lot easier for me to say, "Well, I'm going to try"… But like I say, if the dentist had told me it was due to the smoking in the first place… I could have quit the smoking by now. (Male, 60 years, 15 cigs/day)

This participant felt that previous dentists had not provided sufficient information on smoking and periodontal health. There is an aspect of blame presented, with the participant feeling he would have quit smoking by now if he had been told sooner.

Different to doctor-delivered SCA

The dentist-delivered SCA was received positively by the participants. Many participants felt the dental context of the SCA was different to SCA they had received previously in other settings.

> …it's like, it's, coming from a nurse or a doctor who tells you that your lungs is all… you can't see it, so you just think, "Oh, maybe's not me, I'll be alright", but when you can physically see it, and you can see how it's affected me gums… and affected me teeth and the receding of me gums and the bone… I can't see inside me body, but I can see me teeth… I can see the difference that you's [you] are doing, and I can feel the difference that you's [you] are doing (Female, 52 years, 15 cigs/day)

This participant felt the dentist-delivered SCA was more powerful because she could physically see the damage caused by smoking, unlike the potential damage on her lungs. This participant also identified the personal context and tangible nature of condition as being important, as discussed earlier in this section. The nature of the professional interaction was also noted by some participants.

> ...I would say you've [dentist] had much more impact on me, than even, the doctor… I think because, I can't hide me gums from you… you go to the doctor with an illness, whatever it might... and then it's brought up in conversation but it's only for a few minutes. Yes, he's done his job because

> he's telling you, you know like, you should stop smoking (Female, 58 years, 15 cigs/day)

This participants felt SCA from a general medical doctor was sometimes a routine 'tick box' exercise. However, when delivered by the dentist, the SCA was perceived to carry more influence for many of the previously mentioned themes: personal context and tangible prompts, and positive context. However, dentist-delivered SCA did not have a positive effect on everyone with one participant reporting little impact.

> To tell you the truth it didn't make that much effect, 'cos I was already aware that I shouldn't be doing it in the first place. (Male, 44 years, 30 cigs/day)

4.5 **Discussion**

4.5.1 ***Summary of main findings***

The main findings from interviews related to two broad topics: smoking behaviour and dentist-delivered SCA. In terms of smoking behaviour, this was perceived to be affected by a broad and complex range of influences. Social influences had an important role at both the personal level (family and friends) and at a wider level (social pressure). Some participants were strongly affected by social role and identity and reported being secret smokers. Previous experiences of smoking cessation medications and services were extensive and often negative. Likewise, although a wide range of environmental factors influenced participants, the workplace was particularly strong and often perceived to be a negative influence on quitting attempts or success. Although resources for smoking were sometimes a major consideration (e.g. high cost), many participants felt unaffected by this partly due to sufficient income or access to cheap tobacco. Emotional influences were impactful including stress, 'life events' and fear. Participants were mindful of the addictive and habitual nature of smoking as well as the health consequences, although a small number felt they would be immune or didn't care.

In terms of dentist-delivered SCA, the opportunistic nature of this intervention was important for several of the participants. Putting the advice in a personal context, with tangible prompts, was a powerful motivator for quitting. Framing the advice and subsequent quit attempt in a personal context was seen as useful. Generally the dentist-delivered SCA was received positively, often being compared superiorly to medical doctor-delivered SCA.

4.5.2 ***Relationship to previous research***

Influences on smoking behaviour

Smoking behaviour has many components including initiation, maintenance, cessation and relapse. Since our sample primarily comprised relatively long-term smokers, often with previous experience of quit attempts, the behavioural components of interest are maintenance, cessation and relapse.

Unsurprisingly, our study found that social influences were a strongly perceived influence on smoking behaviour. At a personal level, participants perceived influence from family and friends, usually in a positive context in respect of quit attempts. This is in keeping with the existing literature that has shown the strong influence of the social environment. The majority of the literature has focused on smoking initiation in adolescents or young adults with strong

influences of parents, siblings and peers (Daly *et al.*, 1993; Tyas and Pederson, 1998). Social factors also have important influence on the continuation of smoking (smoking maintenance) with quit attempts more likely if there is a partner who objects to smoking (West *et al.*, 2001) or for those who live in a home with a smoking ban (Li *et al.*, 2011). Conversely, the presence of other smokers, in the form of friends (Richmond *et al.*, 1993) or romantic partners (Murray *et al.*, 1995), often decreases quit success. Interventions that exploit these social influences by involving 'significant others' have unfortunately shown equivocal results (May and West, 2000; Park *et al.*, 2002) and smoking cessation guidelines do not explicitly advocate these at present (Shahab, 2012).

A social factor that was perceived strongly by our participants was the positive influence of younger family members, who were encouraging them to quit smoking. The mean age of our interview participants was 45 years, making it likely that they would have children, nieces/nephews or grandchildren who are teenagers or young adults. There are likely to be significant generational differences with regards to the experience of and attitudes towards smoking. Smoking prevalence rates are now very low in these young age groups with rates as low as 7% being reported for 15 year-olds in England (NHS Digital, 2017). The younger generation will have also experienced very different cultural influences and norms regarding smoking e.g. the smoking ban in public places. There is a notable lack of scientific literature exploring this phenomenon. Although not directly comparable, a recent study found that if parents, who had recently quit smoking, engaged in anti-smoking socialization of their children they lowered their own odds of relapse (Jackson *et al.*, 2016). A study conducted by the Department of Health in 2011 surveyed 1000 children in England about their view on parental smoking (Department of Health, 2011). They demonstrated the strong anti-smoking stance of the 'new smokefree generation of kids' who labelled smoking as 'stupid' and said they would never try a cigarette. The strength of the feeling was confirmed by the fact that many said they would give up all their Christmas presents or pocket money to get their parents to quit. Almost a third of respondents admitted hiding their parent's cigarettes to help them to quit. Future research should confirm the finding of the present study regarding the influence of younger family members on middle-aged quitters and explore the potential to utilise this in behavioural interventions.

These cultural changes have also undoubtedly contributed to the negative societal pressures perceived in the current study. These included a feeling of being in the minority, stigmatisation of smoking/smokers and participants hiding their smoking (secret smokers). These influences emerged particularly strongly, in keeping with the existing evidence that

perceptions of what ought to be done by other people (injunctive norms) rather than perceptions of what is done by other people (descriptive norms) had greater influence on motivation to quit (van den Putte *et al.*, 2005).

The concept of a smoking stigma is extensively discussed in the literature (Stuber *et al.*, 2008; Scheffels, 2009; Tombor *et al.*, 2015; Castaldelli-Maia *et al.*, 2016) and was a powerful influence on the participants, with several trying to avoid stigma by being 'secret smokers'. This has been described recently by Thirlway (2018). Stigma can reduce smoking but can also contribute towards negative consequences such as loss of self-esteem, defensiveness and resolve to continue smoking (Evans-Polce *et al.*, 2015). On lung cancer, for example, public health campaigns have inadvertently increased stigma towards those diagnosed with lung cancer and this has potentially led to deleterious downstream psychological and/or medical outcomes (Riley *et al.*, 2017).

Stigma is also an important concept in periodontitis sufferers. The current study, as well as existing literature (O'Dowd *et al.*, 2010), has identified that periodontitis sufferers are likely to suffer from a range of negative emotions, not directly related to their smoking habit, including stigma, shame, embarrassment and regret about their oral health. Smokers with periodontitis, therefore, potentially suffer from a toxic combination of influences from both smoking and periodontitis and behavioural interventions should be sensitive to this.

Thirlway (2018) provided a convincing argument for smoking stigma operating as a proxy for class stigma. She argues that smoking is being rejected by the middle-class not only because of the health harms but because it has become associated with lower classes; class stigma and smoking stigma have thus become mutually reinforcing. She introduces the Bourdieuian concept of 'cleft habitus' where an individual does not feel 'at home' in their class position. The two examples she provides are the upwardly mobile smoker or the middle-class smoker who is engaged in work/leisure pursuits which have their roots in working-class culture. A pertinent example of the later, from within the current study, involves a professional male who was heavily involved in a working-class culture (motorcycling) and perceiving this as an important influence on his smoking behaviour.

Negative perceptions towards stop smoking medication are a well-recognised barrier towards uptake (Foulds *et al.*, 2009). A range of explanations include concerns regarding the safety of nicotine (in the form of NRT), as well as concerns over the side effects, safety and efficacy of the medications (Etter and Perneger, 2001; Bansal *et al.*, 2004; Hammond *et al.*, 2004; Roddy *et al.*, 2006b). In the current study the participants expressed the strongest concerns regarding

the possible side effects of the medications, referring to their own personal experiences or those of others around them.

The significance of workplace policies and practices on smoking behaviour has been well established, both in terms of prevalence rates (Farkas *et al.*, 2000) as well as differential cessation success rates when exposed to different work environmental factors (Albertsen *et al.*, 2004). Consequently, workplace based interventions have been developed with several potential advantages (peer-group support, targeting those unlikely to access primary care alone and not using personal time) (Cahill and Lancaster, 2014). Thus, it is unsurprising that the current study also identified workplace factors as a significant perceived influence on smoking behaviour. Some particularly useful insights included the perceived importance of the smoking social interaction, with participants concerned about missing out on both important business decisions and 'gossip'.

Governments around the world have used fundamental principles of economics to reduce smoking rates by making it expensive through taxation (Chaloupka, 1999). The evidence generally concludes that increasing prices reduces socio-economic inequalities by hitting the poorest hardest (Giskes *et al.*, 2007; Amos *et al.*, 2011; Chaloupka *et al.*, 2011). The relationship however is not simple due to the addictive nature of the product and presence of 'illicit tobacco'. In the current study, the participants roughly separated into two groups: those for whom the financial cost of smoking was significant and those who reported little perceived influence. In the UK, the issue of 'illicit' tobacco is well established (Action on Smoking and Health, 2017b) and many of our interview participants openly admitted to accessing tobacco via different routes including smuggling ('cheap whites') or bootlegging (legally purchased abroad and transported to another country with a higher tax rate, in amounts beyond those reasonable for personal use).

In keeping with the literature, this study found a strong and complex relationship to emotions. Macnaughton *et al*. (2012) discuss the deep reliance smokers had on their cigarettes, referring to them as 'friends' or 'companions' and this was apparent in our study with several participants turning to them during important life events. Perhaps unsurprisingly the 'pleasure' of smoking is perceived by smokers as a major reason for continued smoking (Ho, 1989) and indeed enjoying smoking is linked to fewer quit attempts (West *et al.*, 2001). This 'pleasure' will be related to the psychoactive effects of nicotine (Benowitz, 2009) but also the complex physiological associations with smoking. Given the public health messages and cultural changes over recent decades, there can be a perception, by some, that continued smoking can be almost solely explained pharmacologically as a nicotine addiction. However,

our study reinforces the powerful influence of 'pleasure' and this should be acknowledged and utilised by policy makers and when designing interventions.

Dentist-delivered SCA

In the current study, participants had positive perceptions about the dentist-delivered SCA, which was in keeping with recent patient surveys (Terrades *et al.*, 2009; Sood *et al.*, 2014). The opportunistic nature of the intervention seemed to carry certain influence, reinforcing existing guidance to HCPs (The National Institute for Health and Care Excellence, 2018). In the particular context of this study, the participants were also receiving a course of periodontal therapy and several participants were shocked by the severity of their periodontal disease; in some cases this appeared to have a synergistic effect with their existing knowledge about smoking harms.

The personal context of the oral health harms appeared particularly important e.g. tooth loss, mobility or staining. NICE guidance on behaviour change (The National Institute for Health and Care Excellence, 2007) highlights a number of concepts for behaviour change based upon the psychological literature and indeed includes 'personal relevance (emphasising the personal salience of health behaviours)'. Another concept they (NICE) identify is 'positive attitude (promoting positive feelings towards the outcomes of behaviour change)' which was another theme identified from the current study. This was perceived particularly powerfully when participants had seen early improvements from their periodontal therapy.

Elsewhere in medicine, the diagnosis of a significant (smoking-related) disease has been associated with an increased quit rate and an ideal time (a 'teachable moment') for SCA interventions (Bassett *et al.*, 2012). The current study would indicate that a smoker with periodontitis who attends the dentist for a course of periodontal therapy would be in an ideal position to receive a SCA intervention. The concept of a 'teachable moment' is described as 'a particular set of circumstances which leads individuals to alter their health behaviour positively' (Lawson and Flocke, 2009). Lawson and Flocke (2009) reviewed the literature on teachable moments, finding they were used across a variety of disciplines but were poorly developed both conceptually and operationally. They identified 81 articles, of which only one was in the dental setting (Stevens *et al.*, 1995) indicating the potential underutilisation within this field and an area of future research.

As well as a general resentment towards authority (e.g. governments) the current study found negative perceptions towards previous dental care and a lack of previous advice. The existing

literature is absent in this field and this should be an area of future research. Future interventions should also consider this in their design.

Finally, with our participants being long-term smokers, many had received previous SCA from other HCPs. Many perceived the dentist-delivered SCA to be different to that from medical doctors. The aspects explored in this section (opportunistic, personal and positive) contributed toward the perception that the dentist-delivered SCA (in the particular context of the study) was more impactful than SCA delivered during a doctor's visit which might have a perception of 'routine' and a 'tick box' exercise.

4.5.3 *Strengths and limitations*

This study is the first qualitative research study to investigate patient perceptions of receiving SCA in the dental setting. The study utilised the TDF, a comprehensive theoretical framework covering all potential hypotheses for behaviour and behaviour change and allowing findings to be matched to theory. The TDF has been used extensively in a wide range of applications, being cited in over 800 peer-reviewed publications (Atkins *et al.*, 2017). As this was a qualitative study, the views expressed are unlikely to be representative of all smokers with periodontal disease. That said, as participants were recruited from a sample taking part in a clinical feasibility study, characteristics of participants were broadly representative of the condition in question (smokers with periodontal disease). For example, the age distribution was typical of those presenting with periodontal disease and smoking measures indicated a moderate nicotine dependence.

However, some limitations of the research are acknowledged. The interviews were conducted within the clinical setting for logistical reasons. The participants were part of a larger clinical study which involved six clinical visits (over approximately six months) and, in order to minimise participant burden and increase compliance, the interviews were scheduled to run prior to an existing study visit, within the dental surgery. This had the potential to influence the participants' responses and in order to minimise any effect the immediate environment was considered. Participants were seated on a sofa, away from the dental chair, and offered a hot drink in order to help them feel at ease. Another consideration was that the interviews were conducted by the research dentist (a limitation of a PhD research project) and again this may have influenced the participants' responses. In an attempt to minimise any influence of this, the participants were reassured at the start of the interview that there were no right or wrong answers and that their care would not be affected in anyway by their responses. A previous study compared interviews by general medical practitioners and a social scientist and found no differences in how frank the participants were, with similar proportions of critical

accounts about health services (Butler *et al.*, 1998). Nonetheless, the qualitative results should be interpreted with this consideration and future research confirm results where required.

4.5.4 *Implications for future research and practice*

The findings of this study offer a detailed understanding of the potential influences on smoking behaviour of smokers with periodontitis attending the dentist. There are a broad and complex range of potential influences which have largely been explored in previous research. The theory-based domains most relevant to this patient group were: social influences, social/professional role and identity, knowledge, environmental context and resources, emotions, nature of the behaviour and beliefs about consequences. Novel themes that were identified comprised: influence of young family members, resentment towards authority/previous lack of support and the potential for the initiation of periodontal therapy to be a teachable moment. Dentist-delivered SCA was well accepted by participants and the important aspects of this were the opportunistic nature, personal context, use of tangible prompts and positive context of the quit attempt. Two novel themes developed around a lack of previous support (from dentists) and comparison of SCA from medical doctors.

Future research should focus on further exploring the novel themes identified to establish their importance in other populations with similar and different disease profiles. Future intervention development should consider the theory-based domains and themes identified as important during their design.

4.6 **Conclusions**

Smokers with periodontitis have a wide range of influences on their smoking behaviour. These largely cover well established themes identified from previous qualitative studies with smokers recruited in clinical settings. Additional concepts were: the influence of younger family members and resentment towards authority/previous lack of support. Dentist-delivered SCA was perceived positively with important aspects being the opportunistic nature, personal context, use of tangible prompts and positive context (of the quit attempt). The findings of this study could be used to inform future intervention development and optimisation.

Chapter 5 **E-cigarettes for smoking cessation within healthcare settings: patients' perceptions and research feasibility. A qualitative interview study.**

5.1 **Abstract**

Background

Healthcare professionals (HCPs) have a professional duty to offer smoking cessation advice (SCA) to their patients who smoke. Most e-cigarette users initiate use independently without advice from a HCP. However, there is likely to be an increasing role for HCPs in supporting patients to stop smoking with e-cigarettes. The aim of this study was to explore the perceptions of individuals attending a healthcare setting towards e-cigarettes, and the acceptability and feasibility of providing e-cigarettes within this setting.

Methods

Theory-based, one-to-one, semi-structured interviews were conducted with a purposive sample of 28 adult smokers with periodontitis who were part of a feasibility randomised controlled trial (n=80). They were randomised (1:1) to receive either usual care (SCA) or usual care plus the offer of an e-cigarette starter kit. Participants were sampled to reflect a range of ages and smoking behaviours. The interview was based on the 12 domains within the TDF to explore perceptions of theory-based influences on smoking behaviour. Interviews also elicited participants' views on dentist-delivered SCA (+/- e-cigarette) and the research process. Interview transcripts were analysed thematically.

Results

Several themes emerged regarding perceptions of e-cigarettes: influence of other e-cigarette users; previous e-cigarette experience; concerns about addiction to e-cigarettes/nicotine; health considerations; and social acceptability. For those who had been offered the e-cigarette starter kit, the main additional themes that emerged included: benefit of behavioural similarities to traditional cigarette smoking (hand-to-mouth, vapour, habit); and influence of flavours. E-liquid flavour choice was dichotomous: for or against tobacco flavours.

Conclusions

Smokers positively perceived the provision of an e-cigarette for smoking cessation within the dental healthcare setting. A wide range of positive and negative perceived influences were identified which could inform future approaches and interventions.

5.2 **Background**

E-cigarettes have been around for just over a decade, hence the public's perceptions are still developing and the focus of much attention. In 2010, there was low awareness of e-cigarettes with almost no smokers using e-cigarettes in quit attempts in England (West *et al.*, 2018). However, by 2014, e-cigarettes were the most common quitting aid, and were used in around a third of quit attempts, which continues to be the case in 2018 (West *et al.*, 2018). Perceptions towards the relative health harms have also changed. In the UK in 2013, only 7% of people surveyed believed e-cigarettes were more or equally harmful as compared to smoking conventional cigarettes but this had increased to 26% in 2017 (Action on Smoking and Health, 2017a). This is unrelated to awareness which has remained high (Brown *et al.*, 2014b; Action on Smoking and Health, 2017a). US data have shown similar trends with a tripling (x 3.1) of those perceiving e-cigarettes to be more or equally harmful than conventional cigarettes between 2012 and 2015 (Majeed *et al.*, 2017). Recent research has identified that many people are concerned about addiction and the addictiveness of e-cigarettes (Thirlway, 2016; Lucherini *et al.*, 2017; McNeill *et al.*, 2018). McNeill and colleagues (2018) called for the 'widespread misperceptions' about the relative risks of nicotine and tobacco to be 'addressed and corrected'.

Research studies on e-cigarettes are still relatively novel and face a unique set of challenges. The first clinical studies on e-cigarettes, which investigated acute effects such as craving and nicotine delivery, commenced in 2008 and were subsequently published in 2010 (Bullen *et al.*, 2010; Eissenberg, 2010; Vansickel *et al.*, 2010). Since then, a large amount of research has been conducted or is in the process of being conducted. Indeed, the recent Cochrane systematic review of e-cigarettes for smoking cessation (Hartmann-Boyce *et al.*, 2016) identified 24 completed studies and 27 ongoing studies. There are many practical issues in conducting clinical research on a novel and varied product such as e-cigarettes e.g. device choice and flavour/strength options. Some research studies have chosen to limit heterogeneity by restricting participants to specific devices, e-liquid flavours and strengths while others have taken a more pragmatic design.

In summary, smokers' perceptions of e-cigarettes are diverse and dynamic. E-cigarette-based interventions within the healthcare and research settings are currently non-optimised. The aim of this study was to explore the perceptions of individuals attending a healthcare setting towards e-cigarettes and the acceptability and feasibility of providing e-cigarettes within this setting.

5.3 **Methods**

A detailed description of the methods is provided in the previous chapter (see chapter 4). Briefly, theory-based, one-to-one, semi-structured interviews were conducted with a purposive sample of twenty-eight participants, fourteen of whom had received the e-cigarette intervention and the remainder of whom had received the control condition (dentist-delivered SCA). Both interventions are described in detail in chapter 3 (see section 3.4.5 and 3.4.6). Briefly, the e-cigarette intervention involved the provision of an e-cigarette starter kit (second generation device, choice of four flavours and four nicotine strengths, see Table 3.2) with participants expected to source and purchase their own supplies after the initial period (2-3 weeks). Participants were sampled to reflect a range of ages and smoking behaviours. The interview schedule (see Appendix S) was developed based upon the 12 domains within the TDF (Michie *et al.*, 2005), ensuring broad coverage of the theories of behaviour change within the interview. The schedule was designed to explore perceived influences on smoking behaviour (chapter 4), views on dentist-delivered SCA (chapter 4), views on e-cigarettes (chapter 5) and feasibility aspects of the research process (chapter 5). A reflexivity statement is provided (see section 6.4.1). This study adhered to the COREQ criteria and a completed COREQ checklist is include (see Appendix T) (Tong *et al.*, 2007).

5.4 **Results**

5.4.1 ***Demographic data***

As described in chapter 4, twenty-eight participants completed baseline interviews shortly after intervention delivery (6 to 48 days after intervention [mean: 25 days]). General views on e-cigarettes were explored with all twenty-eight participants. A more detailed exploration of acceptability issues was conducted for the fourteen participants who had been provided with an e-cigarette starter kit. These fourteen participants were aged 27-60 years (mean age: 44 years). Participants were heavy smokers, all smoking at least 10 cigarettes per day (median number of cigarettes per day: 15; mean eCO: 21ppm) with a moderate level of nicotine dependence (mean FTND: 5). In terms of employment, an almost equal numbers of participants were in professional, intermediate and routine/manual/unemployed categories. There were nine females and five males. Demographic characteristics of the sample are summarised in Table 4.1.

5.4.2 *Overview of themes*

For perceived influences on smoking behaviour, a broad range of themes emerged, covering all 12 of the TDF domains, as presented in chapter 4. Smokers with periodontitis had a range of experiences and perceptions regarding e-cigarettes. Five over-arching themes emerged from the data: influence of other e-cigarette users; previous e-cigarette experience; concerns about addiction to e-cigarette/nicotine; health considerations; and social acceptability of e-cigarettes. When considering those who had been offered the e-cigarette starter kit, three additional themes emerged, comprising the benefit of behavioural similarities with smoking (hand-to-mouth, vapour, habit); the influence of e-cigarette flavours; and technical issues.

Direct quotes are provided and individual participant characteristics (gender, age, average number of cigarettes per day) are shown in brackets following each quote. Supplementary participant quotes are provided in Appendix V.

5.4.3 *Influence of other e-cigarette users*

Many of the participants reported knowing existing users of e-cigarettes. These e-cigarette users almost always acted as a positive influence towards vaping through their conversations or actions.

> …a lot of people I know, they seem, quite positive about it [vaping], and I haven't had any sort of negative, feedback or anything from it so. I think they kind of like think, "Well it's, probably a lot better than a lot of the, junk and stuff that's actually in a normal cigarette. (Male, 45 years, 15 cigs/day)

In this case, the participant knew many e-cigarette users and he perceived them to be positive about vaping. He compared vaping to conventional smoking and felt that the e-cigarette users he knew thought it would be 'a lot better'. Other participants reported similarly positive impressions by observations of people around them.

> A lot of the girls at work, have been really successful on the e-cigarettes… about six or seven of the girls at work have stopped smoking with the e-cigarettes... and they're supportive as well, the girls at work are dead supportive as well. (Female, 52 years, 15 cigs/day)

This participant had experienced many of her workplace friends successfully quitting smoking by using the e-cigarette. The workplace has been previously identified as an important influence of smoking behaviour, as discussed in chapter 4 (see section 4.4.3). At the time of the interview this participant had quit smoking using an e-cigarette (provided in the study). The support of her vaping friends appeared to be an important influence on her continued use of the e-cigarette. Other participants were aware of the positive views of e-cigarette users but still sceptical themselves.

> a lot of people say, "Well it's a lot better than smoking"… the amount of people using them now it's ridiculous, when you actually look around in like a smoking area outside where I work, it is quite crazy how, it's kind of weird, so a lot of people must have a positive views of them as well you know. (Male, 27 years, 15 cigs/day)

This participant had noted the large number of e-cigarette users in his environment and presumed they had positive views on e-cigarettes. However, his choice of language (e.g. ridiculous and weird) suggests he is unconvinced himself and uncomfortable with the number of e-cigarette users.

5.4.4 *Previous e-cigarette experience*

The eligibility criteria for the current study required participants to have not used an e-cigarette regularly, within the 30 days prior to enrolment. However, many had previous personal experience of e-cigarettes from an earlier time period. Over two-thirds (68%) reported prior use of an e-cigarette, of whom around a third (37%) had previously used an e-cigarette on a daily basis. This previous experience varied considerably from having used multiple devices in successful quit attempts (prior to relapse) to having a few puffs on friend's devices. Overall, however, these participants' previous experience of e-cigarettes was predominantly negative.

> I did [previously use an e-cigarette], but it was when they first came out and it used to just leak all over the place in me [my] pocket, and the one that I've got off you is just brilliant because it doesn't leak. And that's why I gave up on, that [previously]." (Female, 52 years, 15 cigs/day)

As in this case, the negative previous experience was sometimes due to technical or practical issues. This participant found the previous device leaked and that caused her to stop using it. In other cases, the negative experiences were related to the sensations experienced by the participant.

> Well I've only tried one, nearly took the back of me [my] throat out, so I just, [laughs]… didn't bother. Cos I think I just had it on the wrong setting… Yeah. I couldn't stop [coughing], I thought I was going to choke… It was horrible. (Female, 57 years, 20 cigs/day)

> … it tasted really funny, you could taste like the, it sounds weird but you could actually taste like electricity in your mouth which was very weird. (Female, 45 years, 10 cigs/day)

These quotes illustrate typical examples of previous negative e-cigarette experiences described by participants. In the first quote the participant experienced an unpleasant sensation in her throat followed by a cough which she described as 'horrible'. The second quote is more related to an unpleasant taste or sensation in the participant's mouth. In other cases, participants went to the effort of sourcing and purchasing e-cigarettes but were put off using them for other reasons other than a negative experience of actually trying it.

> I've bought two different types [of e-cigarette], I bought the ones with the batteries and I've bought the liquid ones… But I've been frightened to use them… I just didn't have the confidence to use them, because you know when you see them on the television... and then there's sort of like, the scare, things... (Female, 58 years, 15 cigs/day)

Concerns about the safety and health harms of e-cigarettes, as reported in the media, are cited by this participant to be reasons for her not using the e-cigarette she purchased. This is explored in subsequent sections (see section 5.4.5 and 5.4.6)

5.4.5 *Concerns about addiction to e-cigarette/nicotine*

Many participants reported concerns about addiction to either e-cigarettes or nicotine. Some expressed this as worries about becoming over-reliant on the e-cigarette with several participants describing a negative image of a 'vaper' with an e-cigarette constantly in their mouth.

> …me [my] brother in law, he's really addicted to his... the vapour pen, and me [my] wife says, she doesn't want me addicted to that… He packed in [smoking] before and just had nothing, but he's packed in this time, and his vapour pen's never out of his mouth… I don't want to be like, walking like around and like having just a vapour pen in my mouth all the time you know what I mean… I'll wean myself off this... (Male, 40 years, 30 cigs/day)

In this quote, the participant describes a family member who he feels had become over-reliant on an e-cigarette. The participant has anxieties about his own use, based upon these concerns, and planned to reduce his e-cigarette use. Some of the participants disliked the idea of still being 'addicted' to something following switching (from tobacco cigarettes to e-cigarettes).

> I know people who have tried e-cigarettes... and they're ridiculous, they just smoke them [the] same as what they did, and they become addicted to them. So it's like, to me, it feels like they're just replacing one addiction for another... (Female, 49 years, 15 cigs/day)

This quote illustrates concerns about simply replacing one perceived addiction with another (e-cigarettes replacing tobacco cigarettes). Worries about a lack of control with e-cigarettes compared to tobacco cigarettes were also voiced.

> ...when I'm smoking [tobacco] cigarettes I know exactly what I'm getting. If I move to a vaper [e-cigarette], I don't really know how much, how much of a hit I'm getting… [If I used tobacco cigarettes] I think it would be easier for me to do it [cut down], to measure what I'm having you know. And less, and less, and less. (Male, 44 years, 30 cigs/day)

Participants were comfortable with their tobacco smoking routine, often having done this for multiple decades. They voiced worries about the lack of control when moving to e-cigarettes, finding 'dosing' difficult to measure. In this case, the participant used this as a reason for continuing to use tobacco cigarettes as they felt they had more control for cutting down.

5.4.6 *Health considerations*

The possible health implications of using e-cigarettes were regularly discussed by participants who expressed a range of opinions. Some participants believed the e-cigarettes to be less harmful to their health than tobacco cigarettes.

> …it's [vaping's] like as if I'm having a cigarette but it's not doing as much harm. (Male, 40 years, 30 cigs/day)

> I feel better for it [switching to e-cigarettes]. I really do. I don't feel like I smell… me [my] mouth's a lot healthier, I'm not wheezing, I'm not coughing, on a morning, it's, I just feel in myself, a lot healthier for packing in real cigarettes and going on to the e-cigarette. It's a massive difference. (Female, 52 years, 15 cigs/day)

These quotes illustrate that some participants held the opinion that e-cigarettes were less harmful than tobacco cigarettes. In the first quote, this appears to be an opinion based on general knowledge whereas in the second quote, the view is based on, or reinforced by, personal experience of improved health after switching to e-cigarettes from tobacco cigarettes. Other participants, and their relatives, had negative views of the health harms from e-cigarettes, often citing media stories.

> I did go on the e-cigarettes for a while… But then me Mam [mum], [fell] seriously ill, and I've actually been looking up this week about it and I think... from what they described, apart from the tumour she had Popcorn lung…Which is part of the e-cigarette… or so they think. (Female, 47 years, 15 cigs/day)

In this example, the participant had a family bereavement of a relative who was a life-long smoker and recent e-cigarette user. The participant has conducted her own research and cites popcorn lung as a health harm from e-cigarettes. Another participant also specifically mentioned popcorn lung in this context.

5.4.7 ***Social acceptability***

The participants expressed a range of perceptions about the social acceptability of e-cigarettes. Some of the participants felt they were socially acceptable with lots of other people using e-cigarettes around them.

> I think at the moment they are [socially acceptable]. I think they've almost become a bit of a fashion trend. A bit trendy at the moment. (Male, 56 years, 20 cigs/day)

Although this participant feels e-cigarettes are socially acceptable, they suggest this might be transient and just a short lived trend. Many participants were comfortable using the e-cigarette around family, friends and in public.

> …I don't feel out of place when I'm using it, I don't feel uncomfortable using it, walking through town or wherever I feel I need it you know. (Male, 27 years, 15 cigs/day)

Others went further and felt the e-cigarette was accepted by smoking culture.

> Yeah, very acceptable because a lot of people… go outside to smoke a cigarette but a lot of people go outside to smoke their e-cig as well… So it's just a case of just general people just standing outside, and I think because you see the smoke, you don't actually think of it as an e-cig, you just think, yeah, you're just fitting in. (Female, 45 years, 10 cigs/day)

This quote illustrates how a smoker has switched to e-cigarettes and feels their social interactions are unchanged. Many participants describe choosing to continue going outside when vaping as if they were still smoking.

> ...I've just slotted it [e-cigarette] in exactly what I would normally do. So, even if it is raining, and sometimes I think, "What are you doing stood outside having a cigarette on a morning, when it's raining?" Like, "How stupid are you?" I've still done it, this morning, I just thought, "No, just go out, and just do it, doesn't matter if you're going to get wet", because really, I could have it [e-cigarettes] in the house, but I don't want to start that. (Female, 35 years, 10 cigs/day)

In this case, the participant is choosing to restrict her use of the e-cigarette to outside areas, even in her home environment. She talks about not wanting to get into a habit of using the e-cigarette inside her house. Other participants chose to use their e-cigarette outside to continue social interactions.

> …when I go out socialising, me [my] friends go out for a cigarette, a lot of places you can't do the e-cig inside, so I've been going out with them but just using that, and it's psychologically [psychological], I'm still smoking with them but obviously not smoking [tobacco] cigarettes. (Female, 45 years, 10 cigs/day*)*

It was important to a number of participants to be able to continue their social routine when switching to e-cigarettes and hence they often chose to self-enforce smoking restrictions on their e-cigarette use. Others describe regulations forcing them to go outside in some environments.

> [At work] Yeah well I still have to go outside with that [e-cigarette]. (Female, 60 years, 15 cigs/day)

Several participants perceived negative perceptions towards e-cigarettes and vapers. Some experienced negative comments personally, while others perceived negative attitudes more widely.

> I suppose it's as frowned upon as a cigarette because, people aren't told how... what's in an e-cigarette. And what's coming out of an e-cigarette. It's certainly, I'm sure, 90% or 95% of people, if you stood next to them with an e-cigarette [they] would shy away as they would with a normal cigarette... When I'm out socially I wouldn't use it. (Male, 58 years, 15 cigs/day)

In this case, the participant describes the negative perceptions towards e-cigarettes they perceived by the general public and how it means they wouldn't use an e-cigarette when out socially. Other participants were uncomfortable about how vaping looked.

> I think if you see someone with a, e-cig, you just know that they used to be a smoker, it just doesn't look attractive. I'll be honest but I don't think either [e-cigarettes or tobacco cigarettes], look attractive… I think they're awful. (Female, 35 years, 10 cigs/day)

> …some of the girls at work, ee, honest to God they've got these, chambers, they're like... I'm like, "Oh my God, do you really need that? (Female, 52 years, 15 cigs/day)

In the first quote, the participant feels vaping, due to it's similarly to tobacco smoking, is unattractive. The second quote focuses on the more complex devices of which a number of participants had negative opinions. One participant was particularly insightful about the changing social norms as the prevalence of e-cigarettes in the population increases. They felt

embarrassment using e-cigarettes in previous quit attempts but this was reduced in the current quit attempt due to more widespread use.

> …when I stopped the last time, for the three months, with it [e-cigarette], there wasn't as many people using them... and I did feel, quite embarrassed, going out and using them… But now, there's such an influx of people actually using them [e-cigarettes] it is quite strange, if you're walking round with a cigarette now rather than the e-cigarette. (Female, 47 years, 15 cigs/day)

5.4.8 *Benefit of behavioural similarities*

Many of the participants reflected that the e-cigarette provided a more fulfilling experience than simply supplying nicotine. Its similarity to tobacco smoking was perceived to be highly beneficial in terms of helping participants to quit.

> It has helped, because, I don't know whether you can appreciate this. It's like having a pen in your hand. You need something to do with your hands. (Male, 58 years, 15 cigs/day)

The most commonly mentioned feature was the tactile sensation of holding something in their hands or the 'hand-to-mouth' action, as illustrated in the above quote. Other sensations such as vapour production or the 'throat hit' were important for several of the participants.

> …and that's where I find it good with the e-cigarette because it replaces that. And you can see the smoke blowing out, you get the throat hit, and it's, it's exactly, a replacement and it's, aye, I've really, found it [quitting tobacco cigarettes] quite, easy, in a way. (Female, 52 years, 15 cigs/day)

The closeness of the actions and sensations of vaping compared to tobacco smoking were important for this participant and reportedly led to an easy quit attempt. The quote below illustrates the strength of feeling and deep consideration some participants had on this topic.

> …you know the e-cigarettes, the good ones you can get now, I find I can get a good inhale and blow a lot of smoke out and that's the type of sensation I like the most. I mean, if I sucked something in, and didn't blow anything out, it doesn't seem as though I had a cigarette. You see?... But although when I get the actual, feel this vapour or whatever it is, it's that which is probably the psychological thing. You see because, just supposing they made a wonder tablet, and I took that tablet, mmm, made us feel like I didn't feel like a smoker, in my head and that would still say, "I want a [breath in/out] this bit", although this wonder tablet stopped that craving for the nicotine shall we say. I believe so, really do. Especially with being smoking for 40 years. It's that sensation. (Male, 59 years, 30 cigs/day)

The behavioural similarities to tobacco smoking were vitally important attributes of the e-cigarette for many of our participants, especially those who have been tobacco smoking for most of their life, as in the above quote.

5.4.9 *Perceptions of the e-cigarette starter kit*

Of the forty participants who were offered an e-cigarette starter kit as part of the feasibility RCT, thirty-nine accepted it (14 of these completed interviews as part of the current study). One participant declined the kit on the grounds that they did not intend to change their smoking behaviour. Generally, participants reported that they found the e-cigarette starter kit acceptable.

> I thought that [the e-cigarette starter kit] was amazing. You know the quality of the e-cigarette that you've given me and the liquids and you've given me the, you know, the tutorial about how to use the e-cigarette. (Female, 47 years, 10 cigs/day)

Furthermore, participants felt the quantity of supplies were sufficient.

> And it does give you a few weeks to get into the routine of it… And I really don't see why, the NHS, whatever [or whoever], should have to pay after

> that… And when you think about it, the amount of money that that is, considering a packet of cigarettes, and how long it lasts, 'cos they [e-cigarettes] do last a long time... (Female, 47 years, 15 cigs/day)

The starter kit was designed to last for 2-3 weeks to give the participants a reasonable trial period and allow them to source their own supplies. The participant in this quote reflects that it lasted long enough for them to get into the routine of using it. She also felt that morally the NHS (or other healthcare provider) shouldn't need to supply any more than this and that the costs of supplies were relatively minimal. Participants reported finding it straightforward to source their own supplies either at pharmacists, corner shops or online.

> I think, using it for a week you're going to decide whether it's going to be the right tool for you to stop smoking or not, so, I think two bottles is fair… Yeah, they're all about aren't they [e-liquids]. You're right, they sell 'em in Boots [pharmacists], they sell 'em in McColl's [newsagents], they sell 'em, everywhere you want to go... (Male, 27 years, 15 cigs/day)

Participants were provided with two batteries and a number reflected on the usefulness of this.

> It's [using the e-cigarette] all about organisation. It's like I've got one battery on charge and I'm using the other one. You know, so when I've finished that one, that one can go straight on. So you haven't got that time that you haven't got an E-Cigarette, that would be the time that you would pick up a [tobacco] cigarette. (Female, 52 years, 15 cigs/day)

This participant also felt the provision of two batteries was essential in preventing relapse to tobacco smoking by ensuring that the e-cigarette was always charged when she needed to use it.

5.4.10 *Influence of flavour*

Participants were provided with a choice of four e-liquid flavours: tobacco, mint, cherry and unflavoured. As part of the trial, they were asked to select two bottles of e-liquid, provided without cost. The most common choice combinations were 'Tobacco & Mint', 'Mint alone',

'Mint and Cherry' and 'Tobacco alone'. Less than half chose a tobacco flavour within their selection. Participants had the choice of four nicotine concentrations (0, 6, 12, 18 mg/ml). The most common choice of nicotine concentration was 18 mg/ml. Full details of the e-liquid choices are presented in chapter 3 (see section 3.4.6 and Table 3.2).

Participants had relatively dichotomous views on flavour preference. The first group held strong preferences against tobacco flavours, believing this might be too similar to tobacco smoking.

> I don't know, 'cos I feel like if you're going to quit [tobacco smoking] you might as well not have cigarette flavour because it's defeating the point, to me anyway. So and I love cherry flavoured stuff so, cherry and minty [is what I used]. (Female, 31 years, 30 cigs/day)

This quote illustrates a participant who preferred the non-tobacco flavours and felt using a tobacco flavored e-cigarette would undermine the quit attempt. As in this case, several participants had a preference for mint flavours.

> I think just with the mint… it's a fresh, it's nice and fresh, on your breath, and that. It's just, it's a pleasant taste. (Female, 52 years, 15 cigs/day)

Mint or menthol flavours were seen as refreshing and spoken about positively by a number of participants. The second group held the view that the e-liquid flavour should be similar to their smoking experience so chose the tobacco flavour.

> I think I chose the tobacco [flavour e-liquid] because I was a little bit frightened that, it would have been too much of a leap from going from no cigarettes to pure mint… But to be honest, the thought now, of going back to tobacco [e-liquid], after using the mint [e-liquid], I didn't want to go back to the tobacco [e-liquid], I didn't want to use the tobacco one, I just want the mint one 'cos I feel as though it's like, fresh… And I didn't, I don't want that stale taste in me [my] mouth again. (Female, 52 years, 15 cigs/day)

Trying to maintain the similarity to tobacco smoking by using tobacco flavoured e-liquid was seen as important by this participant. They then transitioned to mint flavour after using the e-cigarette for a while and subsequently felt that they would be unlikely to go back to the tobacco flavour.

> I went for the normal mixture like the tobacco one and the menthol one as well… I quite like the idea of mirroring the flavours. I think some of these, you know, oh, sweet bubble gum, is ridiculous, because if I want bubble gum, I go and buy bubble gum… I think it should be a, similar flavour, shall we say. (Male, 56 years, 20 cigs/day)

Again this quote illustrates the importance some participants placed on 'mirroring' the flavours they were familiar with when tobacco smoking, which also included menthol cigarettes in this case. This participant spoke about the tobacco and menthol flavours as 'normal' and reflected that the wider range of fruity/sweet flavours were 'ridiculous' which was a common theme in several interviews. However, this was not universal, with some participants keen to try all flavours (this has previously been illustrated in section 3.5.9, Table 3.28 and Table 3.30). Conversely, one participant was keen to avoid any flavour and chose the unflavoured e-liquid.

> …'cos I want to get away from... the tobacco taste. But with the fruit one, like I say, me [my] chest [harsh on chest]. But then I wanted something sweet afterwards… So that's defeated the object for me. 'Cos I don't want to put loads more weight on, so I think, you know, if I don't want anything sweet... (Female, 40 years, 25 cigs/day)

This participant cited several reasons for her choice of the unflavoured e-liquid. She wanted to avoid the tobacco taste, to break away from smoking. She had a previous unpleasant experience of the fruit flavours, which she had perceived to be harsh on her chest and made her want to eat something sweet after use, causing concerns about weight gain.

5.4.11 *Technical issues*

A small number of our participants reported technical issues with the e-cigarettes provided in the study.

> I took my e-cigarette to work on Saturday... and for some reason the damn thing'll not work… I don't know if it's broken... because, when you inhale it… You're supposed to press the button, wait until it, thingies… But then you're getting, your lips is getting covered in oil. (Female, 60 years, 15 cigs/day)

This participant experienced problems with one of the tanks provided as part of the starter kit, having e-liquid leak onto her lips. This was an isolated incident but did highlight that operating the device was not always straightforward for all participants, including those who had never used an e-cigarette prior to agreeing to join the study.

Assistance with operating devices was sometimes obtained from family or friends if technical issues arose.

> My son's 22 and he was, he's been very helpful, as in, you know, showing me what to do with the e-cigarette and making sure it was charged and that I've got enough liquid, and how to put the liquid in, just reminding me again how to do it… I'd arranged everything around… [going] to the caravan, to enable me to quit. I had got up that morning, thought "Right, OK, this is the day I'm going to do it", and then tried to use the E-Cigarette, [but it] didn't work… and I hadn't took [taken] the battery charger with me… Or the charging USB. So then, I rang my son, he said. "Don't worry, when you come back, just do it when you come back". Anyway, when I went back, he tried it and said you haven't clicked it five times before it sort of starts and I was like, "Oh, right, OK", and he said, "Well, start tomorrow". Which I did do, yeah. (Female, 47 years, 10 cigs/day)

The quote highlights the importance of the participant's son in helping her overcome initial issues with using the e-cigarette. Despite being provided with instructions on operating the device by the researcher, a number of participants struggled with the automatic safety lock which requires the button to be pressed 3 times in close succession to deactivate.

5.5 **Discussion**

5.5.1 ***Principal findings***

Interviews with study participants found that a number of factors could influence both positive and negative attitudes towards e-cigarettes. In terms of positive attitudes these were: interactions with existing users (vapers); health benefits; a perception that vaping was seen as socially acceptable; and the social and sensory similarities to tobacco smoking. More negative attitudes were influenced by: personal previous e-cigarette experiences; concerns about addiction; health concerns relating to possible risks of using e-cigarettes; and lack of social acceptability. Interviews also explored the acceptability of the intervention (e-cigarette starter kit). Overall it was perceived to be acceptable with participants, and they were happy to source and purchase their own supplies of e-liquid after the initial period. Interviewees differed in their choice and experience of using different e-liquid flavours, and there were some instances of technical difficulties in using the device, particularly initially.

5.5.2 ***Relationship to previous research***

Overall perception of e-cigarettes

The findings of this qualitative research are largely in keeping with the existing literature in terms of smokers' perceptions and experiences of e-cigarettes.

Some participants in this study had negative previous experiences of e-cigarettes, as some other recent studies have found (Wackowski *et al.*, 2016). Most smokers in the UK who try e-cigarettes do not go on to use them regularly, often because of concerns about risks, lack of understanding about how to use them or the importance of finding the right device, nicotine strength and flavour (McNeill *et al.*, 2018). It is likely that at least some of our participants' experiences would have been with early products, often of poor quality and now superseded by better products. Naïve users are more likely to use first-generation devices, which have been shown to have poor blood nicotine delivery and further contributed to the unrewarding experience (Bullen *et al.*, 2013; Hajek *et al.*, 2017; Ruther *et al.*, 2017). Similarly, there is a steep learning curve for users, with naïve users demonstrating lower blood nicotine levels than experienced users, suggesting the vaping technique needs some practice (Farsalinos *et al.*, 2015; Hajek *et al.*, 2015b).

Another possible explanation for the poor previous e-cigarette experiences is a feature of our study design and eligibility criteria. Those individuals who had a good e-cigarette experience are more likely to have become regular users (with or without tobacco cigarettes) (Wackowski *et al.*, 2016) and therefore have been ineligible for this research study. Therefore, by design,

our participants were more likely to have had suboptimal previous e-cigarette experiences. The participants in the current study were similar to the majority (>80%) of tobacco smokers who are not currently using e-cigarettes (Action on Smoking and Health, 2017a). Over 40% of all current smokers have never tried e-cigarettes (McNeill *et al.*, 2018).

A complementary theme that developed was the concern about addiction to the e-cigarette and/or nicotine, with participants worried about substituting one addiction for another. As previously discussed (see section 1.4.7), there were widespread misperceptions around nicotine addiction and health risks, which appeared to have contributed to smokers having significant concerns about becoming addicted to e-cigarettes. A recent survey in the UK found that concerns about addiction were the most frequent reason for smokers not trying e-cigarettes (Action on Smoking and Health, 2017a). There is relatively little evidence on perceptions of the addictiveness of e-cigarettes (McNeill *et al.*, 2018) although one survey reported that approximately half the participants (adult smokers, ex-smokers or e-cigarette users) thought e-cigarettes were more or equally addictive than tobacco cigarettes (McNeill *et al.*, 2018). In addition, a qualitative study with young adults in Scotland found that they viewed vaping as more addictive than smoking (Lucherini *et al.*, 2017). These young smokers felt in control of their smoking habit but perceived some vapers to be uncontrolled, constantly using their e-cigarettes. They voiced similar concerns to those seen in this study about simply replacing one addiction with another and were concerned about their ability to quit vaping. The demographics of our samples were very different (age and setting), yet this theme was remarkably similar with almost identical quotes from participants. These issues may be applicable to a wide range of smokers and indeed studies with adults have identified similar findings (Vijayaraghavan *et al.*, 2017; Gentry *et al.*, 2018).

Unsurprisingly, given the well-known health harms of tobacco smoking, health considerations of e-cigarettes were a strong theme highlighted by our participants. Some participants perceived e-cigarettes to be less harmful than tobacco, either based on their own experience of switching or on their pre-existing views. Glasser *et al.* (2017) conducted a systematic review and identified a large number of studies (n=188) reporting consumers' perceptions of e-cigarettes. A major reason for use was due to the perception that e-cigarettes were less harmful/less toxic than tobacco cigarettes.

In the current study, others held concerns about the health harms of e-cigarettes which, on at least one occasion, stopped e-cigarette use. This is in keeping with recent surveys which reported that less than half of adults report the accurate perception that e-cigarettes are less harmful than tobacco cigarettes (Action on Smoking and Health, 2017a; Majeed *et al.*, 2017;

West *et al.*, 2018). The proportion stating that e-cigarettes are less harmful than cigarettes are lowest among current smokers who had never used an e-cigarette (33%) and highest (90%) in ex-smokers who had used/tried an e-cigarette (Action on Smoking and Health, 2017a). This difference, based on e-cigarette experience, was also demonstrated by our participants. They experienced positive attitudes towards e-cigarettes from existing users and also perceived them to have been effective in helping people to quit tobacco smoking.

Overall, our participants perceived e-cigarettes to be socially acceptable with participants comfortable using them in a wide range of situations. A recent Royal College of Physicians (RCP) report discussed the potential importance of the 'cultural acceptability' of e-cigarettes (Royal College of Physicians, 2016). For example, social identity as a smoker can be maintained by vapers sharing smoking breaks and being accepted by other smokers. Additionally, vaping is non-medicalised, unlike NRT, and does not imply rejection of smoking or a commitment to quitting. This particular perspective was not identified in the findings from this study, which is, likely because the study was conducted in a medical setting, with the e-cigarette being provided by a clinician.

The sensory similarities between vaping and tobacco smoking were identified by our participants as being particularly important. As previously discussed (see section 1.1.2), smoking addiction is not simply related to the pharmacological effects of nicotine but also to the complex range of stimuli and behaviours associated with nicotine delivery (Rose *et al.*, 2000; Royal College of Physicians, 2016). The hand-to-mouth action, vapour production and 'throat hit' were perceived as advantageous elements of e-cigarette use. One of our participants expressed this when he imagined a 'wonder tablet' stopping the cravings but not being able to replace the sensation of breathing in/out smoke, something he has done for 40 years.

Perceptions of the e-cigarette starter kit

Overall, the participants provided with the e-cigarette starter kit perceived this positively. There were a small number of technical issues experienced by some of the participants. Thirlway (2016) reported that older women in particular found e-cigarettes too much trouble, quickly becoming impatient with product unreliability. In the current study, although numbers were low, there were several older female participants who reported technical difficulties. Young family members played a role in supporting the participants, complementary to the 'social influence and identity' theme described in chapter 3. Participants felt they were provided with an appropriate amount of e-liquid and generally reported few issues in sourcing their own supplies. The provision of two batteries was reported to be useful; however, given

the rapid pace of product development, and battery technology, this may be largely irrelevant for future products and studies. As e-cigarettes and other novel nicotine products continue to evolve and users become more heterogeneous, new and flexible ways of conducting research studies will be required e.g. users might be allowed to experiment with different products (trial and error) (Robson and McNeill, 2017).

Flavour

With regards to e-liquid choice, the participants were guided in respect of nicotine strength based upon the amount they smoked at baseline. Given that they were usually moderate to heavy smokers it is unsurprising that most chose the highest nicotine concentration (18 mg/ml). No guidance was provided however for flavour choice, which was varied (although limited to four flavours in this study). Our findings have important implications for future clinical studies as well as wider regulations. Participants expressed relatively dichotomous views, holding strong preferences either against or in favour of tobacco flavours. Those against tobacco flavours wanted their e-cigarette experience to be different to that of tobacco smoking, choosing mint or cherry flavours in this study. Conversely those in favour of tobacco flavours wanted the familiarity to tobacco smoking. The e-liquid flavour choices of participants in the current study and the opinions they expressed in the interviews are in keeping with flavour preferences observed in the wider population. In the UK overall, the most recent national survey data suggests that the most popular groups of flavours among current e-cigarette users are fruit (29%), tobacco (27%) and menthol/mint (25%) (Action on Smoking and Health, 2017a). Very few current users chose to use no flavours (3%)(Action on Smoking and Health, 2017a), which is in keeping with the current study (1%).

5.5.3 ***Strengths and limitations***

The general strengths and limitations of this research have been previously discussed in chapter 4 (see section 4.5.3). The current study is one of the first pieces of qualitative research to investigate perceptions towards e-cigarettes of patients in a dental healthcare setting. This is an important population demographic to understand as they are potentially susceptible to influence from dental professionals. This study also investigated feasibility issues around e-cigarette research and the findings will have use in future study design. The main limitation of this work is that researcher was the same person who provided the intervention, and this may have influenced responses. Efforts were made to minimize this effect as previously discussed in chapter 4 (see section 4.5.3). Future research should aim to have any qualitative interviews conducted by a separate researcher.

5.5.4 *Implications for future research and practice*

The findings of this study offer a detailed understanding of perceptions towards e-cigarettes of individuals accessing health services, particularly in the dental health setting. Future smoking cessation interventions which use e-cigarettes should consider and, where appropriate, be informed by the identified positive and negative influencing factors. The negative influencing factors offer greatest potential for improving an intervention, by removing barriers. Negative previous personal experiences of e-cigarettes can be a barrier to use and can be addressed by appropriate training and support or the provision of a simple easy-to-use but effective device. Health concerns and concerns about addiction and dosing were also powerful barriers to use and could be addressed within future interventions e.g. by education. Within the healthcare setting, the prescription of an e-cigarette as part of a smoking cessation intervention would help address these barriers, as recently recommended in a government report (House of Commons, 2018). Smokers would have more confidence in a product provided by a healthcare professional, overcoming their previous negative experiences. Likewise, the fact a healthcare professional has deemed it appropriate to provide an e-cigarette would help reduce health concerns and improve confidence. The e-cigarette starter kit provided in this study was highly acceptable to participants and future interventions (research or non-research) should consider utilizing a similar design. A small number of participants (older females) would have benefited from additional support regarding technical issues and future interventions should consider this in their design. An important finding was about flavour choice with dichotomous views for and against tobacco flavours. Interventions and research studies which limit participants to one flavour (usually tobacco) are potentially not using this intervention to its full potential. Ideally participants should have range of choices and these findings support recommendations in the UK (for example from PHE) to research funders to consider moving from studies which have high internal validity to those that have higher generalisability (McNeill *et al.*, 2018).

5.6 **Conclusions**

Smokers accessing dental health services had pre-existing views on e-cigarettes based upon a wide range of influences, and these views may reflect those of patients in other healthcare settings. Understanding these influences could allow e-cigarette interventions in the healthcare setting to be suitably designed and optimised. Smokers positively perceived the provision of an e-cigarette for smoking cessation within the dental healthcare setting. The model of providing an e-cigarette starter kit and requiring users to source their own supplies

after an initial period was deemed acceptable. When designing future interventions, patient choice would be important to consider, including offering a range of flavour options.

Chapter 6 **General Discussion**

6.1 **Background**

Tobacco smoking causes significant morbidity and mortality worldwide. The oral health effects are important and include oral cancer and periodontitis. Many strategies have been proposed and implemented in order to reduce smoking prevalence at both a population and individual level. Advice from health care professionals, such as dental professionals, plays an important role in supporting smokers to quit, although research is lacking on the patients' perspective of such advice. E-cigarette use is now common in many populations, often being used for smoking reduction or cessation and sometimes as a longer-term replacement. It is important to understand the role of e-cigarettes as a smoking cessation aid within the dental setting but also to consider any implications for oral health.

The aim of the PhD research was to explore the behavioural and biological changes when smokers with periodontitis were provided with an e-cigarette. This chapter discusses how the PhD research contributes to the existing evidence base and considers its strengths and limitations. The implications of the research findings are discussed along with recommendations for future research.

6.2 **Main findings**

A series of mixed methods studies were conducted to explore the behavioural and biological impacts of e-cigarettes within the dental setting. Firstly, a systematic review was conducted to clarify the evidence with regards to the effects of nicotine on oral cells *in vitro*. Secondly, a feasibility study explored the delivery of an e-cigarette within the dental setting by conducting a pilot RCT with process evaluation.

6.2.1 ***Systematic review on in vitro effects of nicotine***

The systematic review identified a large number of studies investigating the *in vitro* effect of nicotine on oral cells. There was high heterogeneity and the studies were often of poor/moderate quality. Cell viability was the most studied variable and the results indicated that, at physiological concentrations (i.e. GCF and salivary concentrations of nicotine seen in tobacco smokers, NRT users, e-cigarette users and non-users), nicotine was not cytotoxic to periodontal cells *in vitro* (salivary levels in smokeless tobacco users was high enough to

achieve cytotoxicity). Nicotine may have effects on other cell functions although evidence was contradictory.

These findings support the supposition that nicotine is not the damaging agent in tobacco smoke. Hence, nicotine's use in the form of NRT or e-cigarettes should not be discouraged based on the premise that there is evidence that nicotine is cytotoxic to oral cells.

6.2.2 *Pilot trial*

The pilot RCT successfully recruited 80 smokers with periodontitis of whom, 58 completed the study, giving a 73% retention rate. The e-cigarette intervention was well received with 90% using it at the quit date and over half using it for the duration of the study. Several participants chose to diverge from the recommended brand of e-liquid and an interesting observation is that these individuals made up almost all of the quitters in the intervention group. One in five participants in the control group used an e-cigarette, against instructions, an important variable to consider when designing future research.

Outcome measures were successfully completed in clinic but a weekly smoking questionnaire had poor completion rates. Smoking outcome measures demonstrated harm reduction (reduction from baseline to 6 months of eCO) of 6 ppm [95% CI: 1-10] and 12 ppm [95% CI: 8-16] in the intervention and control groups respectively; rates of abstinence (carbon monoxide verified continuous abstinence for 6 months) for the two groups were 5% [95% CI: 1%-17%] and 15% [95% CI: 7%-29%]. The oral health outcome measures demonstrated slight improvement in the intervention group compared to the control group.

Modifications to the study design were proposed, such as: not collecting research data at the 3-month review visit, introducing an incentive for attendance at post-treatment follow-up visits, not using a weekly questionnaire, consolidating the number of outcome measures collected, considering a wait list control design and conducting part of the research in a primary care setting.

6.2.3 *Qualitative interviews*

A broad and complex range of factors were perceived to influence smoking behaviour in individuals with periodontitis, including: social influences, social/professional role and identity, knowledge, environmental context and resources, emotions, nature of the behaviour and beliefs about consequences. Dentist-delivered SCA was positively perceived and several important aspects were perceived by patients, comprising: opportunistic nature, personal

context and tangible prompts, positive context of cessation attempt, lack of previous support and differences by comparison with doctor-led SCA.

6.3 **Relationship to previous research**

Each chapter has individually considered how the findings relate to previous research. However, it is important to compare the methods used in the PhD research to the existing evidence base.

The feasibility study with embedded pilot RCT provided a detailed understanding of the viability of delivering and studying the intervention in question, with several important implications for the future definitive study. The design and reporting of the study has followed recommendations such as the CONSORT checklist for pilot and feasibility studies (Eldridge *et al.*, 2016); Robson and McNeill (2017) and TiDieR checklist for reporting interventions (Hoffmann *et al.*, 2014). Lancaster *et al.* (2004) previously reviewed the medical literature and concluded that pilot trials were often poorly conducted and inadequately reported. Although a systematic review of the dental literature has not been undertaken, it is clear that very few, if any, dental feasibility or pilot studies follow these principles and standards. In chapter 3, I presented an evaluation of the dental pilot studies investigating e-cigarettes and oral health, concluding that they were poorly reported and had several fundamental weaknesses. We recently wrote a letter to a journal editor (Holliday *et al.*, 2018) highlighting concerns about a so-called pilot study published in their journal (Javed *et al.*, 2017a) and called more broadly for journals to ensure pilot studies comply with minimum reporting standards.

In chapter 3 (see section 3.2) I discuss the limitations of the pilot study by Wadia *et al.* (2016) in which they inappropriately concluded that there was a statistically significant increase in gingival inflammation when smokers switched to vaping. However, an increase in gingival inflammation when smokers quit is a well-established clinical observation and can likely account for the findings of this study, particularly given the lack of a control group. Indeed, there is an inverse interpretation of the results; that e-cigarette use had no effect upon the normal rapid recovery of the inflammatory response following smoking cessation. The results from the pilot trial conducted during this PhD, although not suitably powered for statistical testing, do not support the conclusion of Wadia *et al.* (2016). Unfortunately, a recent national review (Stratton *et al.*, 2018) has included this study (Wadia *et al.*, 2016), and without disease-specific expertise on their review panel to interpret the results, they have concluded that e-cigarette aerosols can ‘induce gingival inflammation in the oral cavity’. A separate

national review (Byrne *et al.*, 2018) has repeated these conclusions, reinforcing and disseminating them further. This example highlights the responsibility on researchers and journal editors to ensure their studies follow the highest standards of design and reporting [e.g. CONSORT extension for pilot and feasibility trials (Eldridge *et al.*, 2016)] in order to ensure research rigour and minimise potential for misinformation. Generally, there is a need to raise awareness of pilot and feasibility study methodology and reporting within dental research and improve standards. Concerning the specific topic of e-cigarettes and oral health, the current study represents the first properly conducted pilot trial in the field. The findings from this study will allow for a well-designed and efficient definitive study in order to answer the research question.

When designing a trial it is important to consider the impact on applicability of every design decision. The PRagmatic Explanatory Continuum Indicator Summary 2 tool (PRECIS-2) allows trialists to ensure their study design is consistent with the intended purpose by scoring 10 aspects of the study design (Loudon *et al.*, 2015). The tool produces a useful illustration, the PRECIS-2 wheel, which demonstrates to trialists if their trial design will support the overall aim. It also identifies consistency between domains (the smoothness of the wheel) with regards to explanatory or pragmatic approaches.

The pilot RCT in this PhD was designed to be at the pragmatic end of the explanatory-pragmatic spectrum (Schwartz and Lellouch, 1967; Thorpe *et al.*, 2009; Loudon *et al.*, 2015) but formal testing using the PRECIS-2 wheel was only completed retrospectively. Figure 6.1 presents the PRECIS-2 wheel for this study and Table 6.1 provides the explanation and rationale for each score. Overall, the trial was rather pragmatic, scoring the highest possible pragmatic scores in several domains. However, several domains were identified as less pragmatic, specifically: the setting, flexibility of delivery and participant follow-up. A future definitive study which aimed to have a pragmatic approach should aim to review these areas to improve consistency (and improve the smoothness of the wheel). For example, the setting for a future definitive study could be conducted in both secondary and primary care environments in keeping with the intended environments of the intervention in usual care. Additionally, the delivery of the intervention could be more flexible, perhaps delivered by a dental nurse with little additional training on the topic and with little instruction.

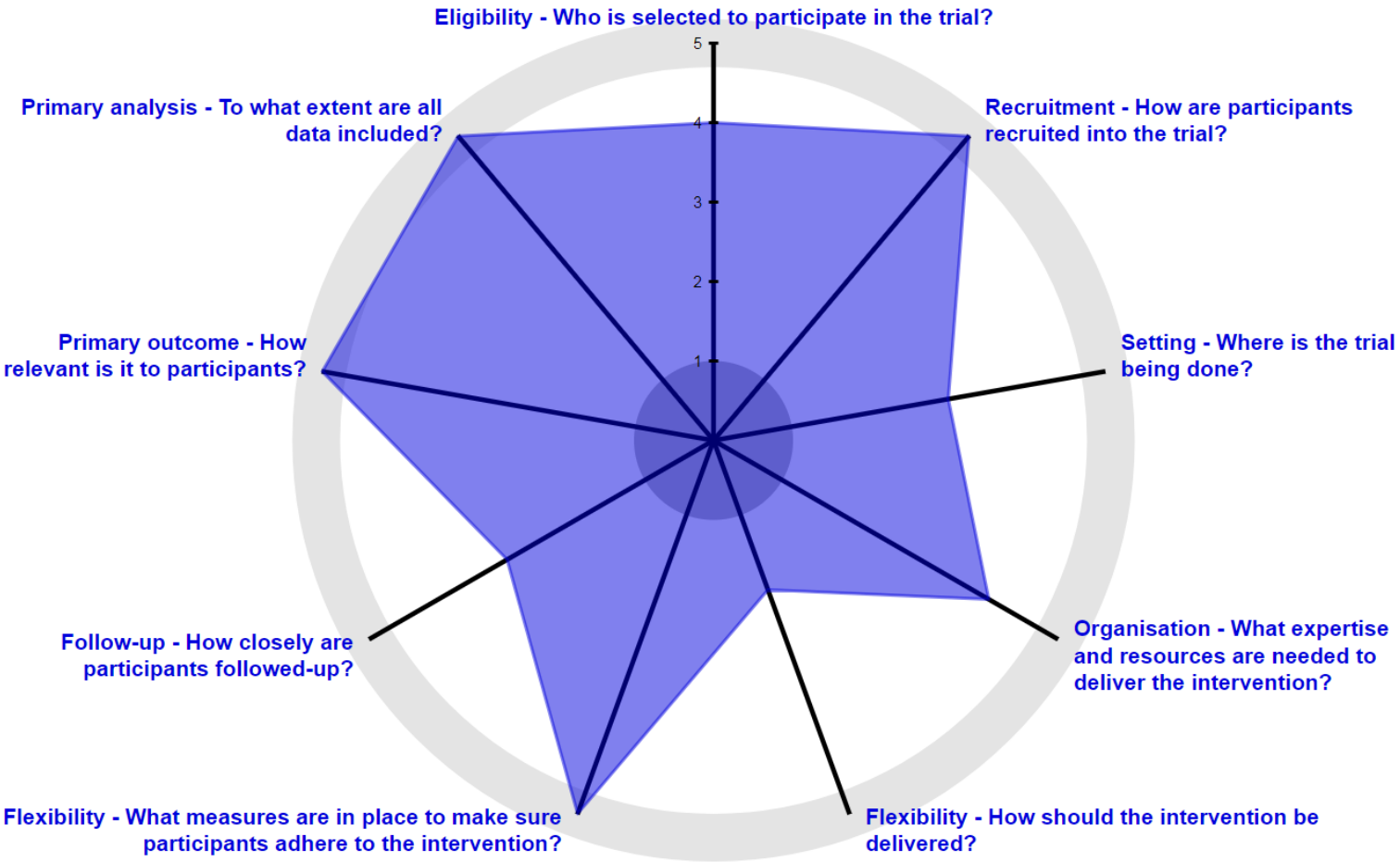

Figure 6.1 The PRECIS-2 wheel for the pilot RCT.

PRECIS-2 domain	Rationale for score
Eligibility	The study had pragmatic eligibility criteria, very similar to those in usual care. There was no 'willingness to quit' criterion, similar to the universal approach of smoking cessation interventions taken in usual care. The criteria for age were broad, only having a lower cut off (18 years of age) in keeping with the legal age restrictions around e-cigarettes in the UK. The medical exclusion criteria were in keeping with the instructions provided with NRT and e-cigarettes. Our study included a lower smoking threshold (≥10 factory-made cigarettes/day or 7g [0.25 oz) loose tobacco/day or 14 hand-rolled cigarettes/day) which is not present in usual care (all smokers are provided smoking cessation interventions regardless of their smoking amount). We also excluded smokers who had used a e-cigarette for more than two days in the last 30 days, which may not represent usual care when these smokers would be included. A score of 4 was awarded as eligibility was very similar but not identical to usual care.
Recruitment	We recruited through usual care environments in an opportunistic manner. Participants were only recruited after they presented to a dental clinic on their own behalf without any overt recruitment effort. We recruited from a range of primary care and secondary care dental clinics. A score of 5 was awarded as we recruited from a diverse range of usual care appointments.
Setting	A hub-and-spoke design was utilised with participants being identified in a number of environments but the research study being conducted in a secondary care dental setting. The single centre design limits the generalisability of the results and is more explanatory (although a single centre design was appropriate for a pilot study, with the resource constraints associated with a PhD). The results of the study will be applicable to secondary care (where the study was conducted) but also to primary care and future studies should have a primary care component to ensure applicability of the results. A score of 3 was awarded due to the single centre secondary care setting.
Organisation	Identical organisation to usual care with same staff. The e-cigarette intervention delivered in this trial was relatively pragmatic. A simple starter kit was provided designed to replicate what might be available on prescription in the future. Staff required some limited additional training and delivered a short tutorial to participants on the e-cigarette which largely followed the instruction manual. A score of 4 was awarded as the organisation was very similar, but not identical to usual care.

PRECIS-2 domain	Rationale for score
Flexibility (delivery)	Protocol driven- The interventions and co-interventions delivered followed a detailed protocol. Adherence and compliance- Interventions were audio-recorded to check for compliance but no measures were in place to improve compliance. A score of 2 was awarded as there was a rather explanatory approach to intervention delivery.
Flexibility (adherence)	There was full flexibility in how participants engaged with the intervention. There were no special measures to enforce engagement or compliance. Participants were instructed to continue using the same brand of e-liquid (as recommended in the manufacturer's instructions), although there were no consequences for violating this. A score of 5 was awarded as a highly pragmatic approach was taken to intervention adherence.
Follow-up	The number of follow-up visits was as would be as expected in usual care. However, the duration of these visits was longer than in usual care due to the collection of research data (some would be part of usual care but some is beyond what would be collected in usual care). Participants were also contacted if they failed to keep trial appointments (in order to improve retention) but this would be over and above that conducted in usual care. A score of 3 was awarded as the study had both explanatory and pragmatic aspects to participants follow-up.
Primary outcome	The primary outcome was smoking abstinence which is of obvious importance to participants and commissioners of care. This outcome was measured by self-reporting and with expired air carbon monoxide readings, the same as usual care. A score of 5 was awarded due to the highly pragmatic approach. N.B. This was a pilot trial and hence the study objectives were to do with assessing the viability of delivering and evaluating the intervention. The primary outcomes for the definitive study would likely be smoking abstinence and periodontal health.
Primary analysis	An intention-to-treat analysis with all available data. A score of 5 was awarded due to the highly pragmatic approach.

Table 6.1 Rationale for PRECIS-2 domain scores.

When specifically considering the e-cigarette intervention, previous clinical studies have taken a range of approaches. Many studies, especially earlier studies or those measuring specific biological outcomes, often chose to follow a traditional tightly controlled design with regards to the e-cigarette intervention. They have provided the e-cigarette device (Bullen *et al.*, 2013; Caponnetto *et al.*, 2013; Adriaens *et al.*, 2014), sometimes with spare batteries (Bullen *et al.*, 2013) and a substantial e-liquid supply: 2 months (Adriaens *et al.*, 2014), 12 weeks (Caponnetto *et al.*, 2013), or 13 weeks (Bullen *et al.*, 2013). There was often little flexibility concerning intervention adherence with participants having no choice of e-liquid strength and/or flavour (Bullen *et al.*, 2013; Caponnetto *et al.*, 2013; Adriaens *et al.*, 2014). A choice of e-liquid flavours is rare in research studies, with most only providing tobacco flavour (Caponnetto *et al.*, 2013; Adriaens *et al.*, 2014) or unflavoured (Fraser *et al.*, 2015). Some studies offered a choice between tobacco and menthol (Lopez *et al.*, 2016; Beebe, 2017).

The recent Cochrane systematic review (Hartmann-Boyce *et al.*, 2016) acknowledged the challenges of making a 'blanket assessment of cessation efficacy' due to the large variation in the e-cigarette intervention. Robson and McNeill (2017) argue that strict eligibility criteria and requiring fidelity to an intervention (e.g. type, dose, duration and frequency) is discordant with what happens in real life. Hence, research studies have started to shift towards the pragmatic end of the explanatory-pragmatic spectrum when considering the e-cigarette intervention. For example, Hajek *et al.* (2015c) provided an e-cigarette starter kit, with a 2-week supply of e-liquid (18 mg/ml, tobacco flavour) and expected participants to source their own e-liquid beyond this. The current study chose a similar approach, although being even more pragmatic by providing a choice of four e-liquid flavour and strength options. Other studies have taken an even more pragmatic approach, allowing some elements of trial and error by participants when selecting the e-cigarette (Bauld *et al.*, 2018) as recommended by McNeill *et al.* (2018).

The outcome measures with regard to smoking cessation and periodontal health used in this study, and proposed for the future study, fit with the core outcome sets recommended by the COMET initiative (T Lamont, personal communication, 21 August 2018) (West *et al.*, 2005a; Glenny *et al.*, 2012).

6.4 **Strengths and limitations**

The specific strengths and limitations of my research have been discussed in each chapter. However, this section will acknowledge the main strengths and limitations of the research as a

whole. A major strength is that the research has been conducted in a rigorous manner following the relevant standards for each methodology. The systematic review followed the PRISMA statement and checklist; the pilot RCT followed the CONSORT extension for pilot and feasibility studies, with interventions being described using the TiDieR checklist; and the qualitative interviews employed the TDF framework and followed the COREQ checklist. The mixed-methods approach combining the quantitative pilot trial with qualitative interviews has allowed us to gain different and more insightful perspectives on the findings. A good example of this is the e-liquid flavour choices observed in the pilot trial being enriched by the participants' perspectives arising in the interviews.

This study was the first qualitative research study to investigate patient perceptions of receiving SCA in the dental setting and the theory-based findings will be important influences to consider when designing interventions.

A strength of the research was to approach the feasibility study with the widest perspective considering all the possible aspects of a future definitive trial. Specifically, the work conducted around identifying, negotiating and helping form solutions for the regulatory barriers that existed for e-cigarette research was fundamentally important.

A particular strength of this project was the multi-disciplinary nature of the supervisory team. Although I have led the research, the specialist input and advice from a range of disciplinary experts has added huge value to this project, directing me to relevant literature and challenging my and each other's thinking.

There are some important limitations of the research presented in this PhD that should be acknowledged. The systematic review limited its scope to nicotine (excluding cotinine) and to four domains in order to keep the review focused and manageable. The pilot RCT had challenges with control group contamination, moderate to high participant attrition rates, and differential baseline disease severity between groups. The qualitative interviews had some limitations concerning the setting of the interviews.

6.4.1 *Reflexivity (positionality) statement*

Reflexivity is an important component of qualitative research and is the process of reflecting on how the researcher could influence the research conduct and findings. This is particularly important on the topic of this thesis (e-cigarettes) as it is still an emerging topic, on which strong and divergent views are held.

For this study I was the main researcher, a 32-year-old white male from a middle class background. I have been educated to degree level and live in the north-east of England. I have conducted a range of research projects on the topic of oral health (particularly periodontal diseases) with the aspiration of improving the health of patients and the wider public. On the subject matter of tobacco, I am a never-smoker but have experienced first-hand the extensive health harms that can result from use. My clinical work involves treating patients with severe periodontal disease and oral cancer, both of which have tobacco smoking as a major risk factor. My research aspirations are to help develop or optimize interventions to help smokers quit/reduce and limit their health harms. Regarding e-cigarettes, I first became interested in the subject matter in 2013 after treating a patient using a device. Since then I have taken a close interest and I am currently conducting several research projects on the topic (including this PhD). My opinion is that conversations based around whether e-cigarettes are 'good or bad' are overly simplistic. There are many variables to consider but for the subjects of this study (adult smokers, often with several failed quit attempts), the use of e-cigarettes as a quit aid or longer term substitute appears to be a sensible and potentially effective approach. I am open-minded to the developing evidence base and would describe my current position as 'cautiously positive'. For the duration of this study (2016-2018) my opinions have remained stable. My opinions are in keeping with the majority of the experts and organizations in this field, although I am aware that there are a wide range of viewpoints globally. I have concerns about the lack of oral health research conducted so far and would like to see oral health considerations play a more prominent role in this field. I feel passionately about research rigour and have generally been disappointed by the quality of the research so far published on the topic of oral health and e-cigarettes. I have no financial conflicts of interest and am funded by a NIHR fellowship. I have never received funding from a tobacco or e-cigarette manufacturer.

6.5 **Implications for future research**

The primary outcome from the feasibility study is the conclusion that a future definitive study (in the form of a pragmatic RCT with economic evaluation and qualitative process evaluation) would be viable and worthwhile. The pilot RCT identified many aspects of study design that will help deliver an optimum definitive study (as detailed in chapter 3). Some of the most significant findings are now considered.

Regarding recruitment, a rate of five participants per month can be expected for a dental research centre. When utilising a hub-and-spoke design (i.e. several locations identifying

potential participants and one hub location conducting the research) there were lower rates of engagement and retention from those participants coming from primary care. Future research designs may consider conducting the research in several locations, including primary care. Including a primary care aspect to the research design will also increase applicability and make the design more pragmatic.

The pilot RCT observed considerable e-cigarette use by the non-e-cigarette control group and a definitive study should consider study designs to reduce or account for this. For example, a wait list control design may be useful, although will likely have implications for the control group abstinence rate.

The e-cigarette intervention, in the form of a starter kit, delivered in this study worked well and represents a highly pragmatic approach i.e. it resembles what might be available on prescription in the future or what a patient might buy over the counter when initiating use after advice from a dental professional. The importance of having a range of flavours was highlighted, both tobacco and non-tobacco options. Our findings also suggest that experimenting with different products, brands and flavours was an important aspect of the intervention. In the pilot RCT, these 'experimenters' made up all but one of the quitters. Future trials should allow participants to source their own products following provision with the starter kit.

The weekly smoking questionnaire was poorly completed in the pilot RCT and should not be used in future research without modifications. Incentives should be considered to maximise participant retention following completion of the periodontal treatment.

A sample size calculation based upon co-primary outcomes, smoking abstinence rates (RS6-eCO) and periodontal health (PPD or percentage of sites with PPD ≥5 mm), requires 674 participants. Once participant attrition and eligibility rates are accounted for, 1162 potentially eligible participants will need to be approached. A multi-centre RCT including both primary and secondary care locations would be a suitable study design to achieve these participant numbers.

6.6 **Overall conclusions**

Nicotine is likely not to be the harmful component of tobacco smoke on oral health. Patients perceive dentist-delivered smoking cessation interventions positively. E-cigarettes may represent an effective option for smoking cessation within the dental setting and a future definitive study should evaluate this. This study should be designed upon the findings of the pilot RCT presented in this thesis.

Appendix A Supplementary Figure S1- PRISMA Checklist

Section/topic	#	Checklist item	Reported in section No.
TITLE			
Title	1	Identify the report as a systematic review, meta-analysis, or both.	Chapter 2 (Identified as a systematic review)
ABSTRACT			
Structured summary	2	Provide a structured summary including, as applicable: background; objectives; data sources; study eligibility criteria, participants, and interventions; study appraisal and synthesis methods; results; limitations; conclusions and implications of key findings; systematic review registration number.	2.1
INTRODUCTION			
Rationale	3	Describe the rationale for the review in the context of what is already known.	2.2
Objectives	4	Provide an explicit statement of questions being addressed with reference to participants, interventions, comparisons, outcomes, and study design (PICOS).	2.3 and Table 2.1
METHODS			
Protocol and registration	5	Indicate if a review protocol exists, if and where it can be accessed (e.g., Web address), and, if available, provide registration information including registration number.	2.7
Eligibility criteria	6	Specify study characteristics (e.g., PICOS, length of follow-up) and report characteristics (e.g., years considered, language, publication status) used as criteria for eligibility, giving rationale.	2.3
Information sources	7	Describe all information sources (e.g., databases with dates of coverage, contact with study authors to identify additional studies) in the search and date last searched.	2.3
Search	8	Present full electronic search strategy for at least one database, including any limits used, such that it could be repeated.	2.3.2
Study selection	9	State the process for selecting studies (i.e., screening, eligibility, included in systematic review, and, if applicable, included in the meta-analysis).	2.3.3 and Figure 2.1
Data collection process	10	Describe method of data extraction from reports (e.g., piloted forms, independently, in duplicate) and any processes for obtaining and confirming data from investigators.	2.3.3
Data items	11	List and define all variables for which data were sought (e.g., PICOS, funding sources)	2.3

Section/topic	#	Checklist item	Reported in section No.
		and any assumptions and simplifications made.	
Risk of bias in individual studies	12	Describe methods used for assessing risk of bias of individual studies (including specification of whether this was done at the study or outcome level), and how this information is to be used in any data synthesis.	2.3.4
Summary measures	13	State the principal summary measures (e.g., risk ratio, difference in means).	NA
Synthesis of results	14	Describe the methods of handling data and combining results of studies, if done, including measures of consistency (e.g., I^2) for each meta-analysis.	2.3

Appendix B Supplementary Table S1: Reasons for exclusion of reviewed full-text studies

Study	Reason for exclusion	Further details
Almasri et al. (2007)	Non-relevant outcome assessed	Measured cytokine expressions rather than production or secretion
Al-Qattan & Soory (2012)	Non-relevant cell types & assays	Periosteal fibroblast, osteoblast; metabolic activity & DHT yields
Argentin & Cichetti (2006)	Non-relevant outcome assessed	Mechanisms of nicotine-induced genotoxicity (nitric oxide; caspase-1)
Austin *et al.* (2001)	Non-relevant outcome assessed (indirect)	Indirect assessment of HGF adhesion (integrin β_1 expression)
Chang *et al.* (2003a)	Non-relevant outcome assessed	Mechanisms of nicotine-induced genotoxicity (c-fos; thiols)
Chang *et al.* (2003b)	Non-relevant outcome assessed	Mechanisms of nicotine-induced cytotoxicity (COX-2 expression)
Chang *et al.* (2005)	Non-relevant outcome assessed; nicotine not a variable	Mechanisms of nicotine-induced cytotoxicity (heme oxygenase-1)
Cogo *et al.* (2009)	Non-relevant cell types	Human epithelial cell (KB, cervical adenocarcenoma) bacterial colonisation
Fang & Svoboda (2005)	Non-relevant outcome assessed	HGF differentiation into myofibroblasts
Gao *et al.* (2014)	Non-relevant outcome assessed; nicotine not a variable	HGEC genotoxicity; nicotine is control vs. smokeless tobacco
Giannopoulou *et al.* (2001)	Non-relevant outcome assessed (indirect)	Effect of nicotine-exposed HGEC on HGF proliferation & collagen production
Hanes *et al.* (1991)	Non-relevant outcome assessed	Binding, uptake & release of nicotine by HGF
Ito *et al.* (2013)	Non-relevant cell types & outcomes assessed	Ca9-22, HSC3 cell (oral squamous cell carcinoma) expression of LDL receptor
Jeong *et al.* (2009)	Nicotine not an isolated variable	Nicotine always varied alongside LPS
Katz *et al.* (2005)	Non-relevant outcome assessed; nicotine not a variable	RAGE upregulation in HGF exposed to nornicotine
Katz *et al.* (2007)	Non-relevant outcome assessed; nicotine not a variable	RAGE upregulation in HGEC exposed to nornicotine
Kirschneck *et al.* (2015)	Non-relevant outcome assessed (indirect)	Indirect assessment of cytokine production (mRNA for IL-6 & COX-2)
Leonardi *et al.* (1999)	Non-relevant outcome assessed	Immunocytochemical expression of α_2 integrin by GF
Martinez *et al.* (2005)	Non-relevant cell types	Rat fibroblast viability
Peacock *et al.* (1993)	Non-relevant outcome assessed (indirect)	Effect of nicotine-exposed HGEC on HGF viability/attachment

Pi *et al.* (2010)	Non-relevant outcome assessed	Mechanisms of nicotine-induced genotoxicity (COX-2 expression, nitric oxide synthase induction)
Sadaoka *et al.* (2013)	Non-relevant outcome assessed	Chromogranin A production in HPDLC exposed to nicotine
Snyder *et al.* (2002)	Non-relevant outcome assessed (indirect)	Indirect assessment of HGF adhesion (integrin β_1 expression)
Soory & Suchak (2003)	Non-relevant outcome assessed	Nicotine modulating HGF metabolism of testosterone to DHT
Tinti & Soory (2012)	Non-relevant outcome assessed	Mechanisms of oxidative effect of nicotine on HGF (DHT yields)
Tinti & Soory (2013)	Non-relevant outcome assessed; nicotine not an isolated variable	Mechanisms of oxidative effect on HGF; nicotine always varied alongside H_2O_2
Yu *et al.* (2016)	Non-relevant cell types	HaCAt (immortalised keratinocyte from human skin) viability & genotoxicity

HGEC= Human gingival epithelial cell, HGF= Human gingival fibroblast, HPDLC= Human periodontal ligament cell.

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Appendix C Supplementary Table S2: Characteristics of included studies: cell type, cell origin, investigations, quality assessment according to modified CONSORT checklist, funding source(s) and location of first author.

Study	Cell types investigated	Cell Origin				Investigations completed				Quality assessment score	Funding source	First author location
		Primary cells or cell line?	Location or origin?	Smoker?	Age (years)?	Cell viability	Cell attachment/ adhesion	Cell proliferation	Cytokine production			
Alpar *et al.* (1998)	HPDLC + HGF	Primary	Attached gingiva and molar root ligament	Smokers & non-smokers	Not specified	X		X		6	No details provided	Germany
Argentin & Cicchetti (2004)	HGF	Cell line	Coriell Cell Repository, AG09429; apparently healthy Caucasian female	Not specified	25	X		X		8	Ministry of Education, University & Research (MIUR) grant	Italy
Chang *et al.* (2001)	HPDLC	Primary	Orthodontic premolar extractions, healthy individuals	Not specified	Not specified	X				8	Chung Shang Medical and Dental College	Taiwan
Chang *et al.* (2002)	HPDLC	Primary	Orthodontic premolar extractions,	Not specified	Not specified	X		X		8	Chung Shang Medical and Dental College	Taiwan

Study	Cell types investigated	Cell Origin				Investigations completed				Quality assessment score	Funding source	First author location
		Primary cells or cell line?	Location or origin?	Smoker?	Age (years)?	Cell viability	Cell attachment/ adhesion	Cell proliferation	Cytokine production			
			healthy individuals									
Checchi *et al.* (1999)	HGF	Primary	Periodontal surgery	Smokers & non-smokers	16 - 25 and 40 - 65	X		X		9	Consiglio Nazionale delle Ricerche (National Research Council, Italy)	Italy
Ciapetti *et al.* (1999)	HGF	Primary	Periodontal surgery	Smokers & non-smokers	16 - 65	X		X		8	No details provided	Italy
Desjardins & Grenier (2012)	HGF + HOEC	Primary (HGF)/ Cell line (HOEC)	HOEC: transformed (immortalised) GMSM-K from University of North Carolina. HGF: gingival biopsy from Caucasian male, "normal" health status, HGF-1, American Type	Not specified	28 (original source of HGF)	X			X	8	Fondation de l'Ordre des Dentistes du Québec; Canadian Institutes of Health Research	Canada

Study	Cell types investigated	Cell Origin				Investigations completed				Quality assessment score	Funding source	First author location
		Primary cells or cell line?	Location or origin?	Smoker?	Age (years)?	Cell viability	Cell attachment/ adhesion	Cell proliferation	Cytokine production			
			Culture Company (ATCC).									
Dinos *et al.* (2015)	HGF	Primary	Gingival biopsy, healthy individuals, no local inflammation	Non-smokers	Not specified	X		X*		8	No details provided	USA
Esfahrood *et al.* (2015)	HGF	Cell line	Pasteur Institute of Iran, C-165 – further details unavailable	Not specified	Not specified	X	X			9	"None declared"	Iran
Fang & Svoboda (2005)	HGF	Primary	Crown lengthening surgery, healthy individuals	Non-smokers	Not specified			X*		9	Baylor Oral Health Foundation; National Institutes of Health; Tobacco Endowment Fund, Texas A&M University	USA

Study	Cell types investigated	Cell Origin				Investigations completed				Quality assessment score	Funding source	First author location
		Primary cells or cell line?	Location or origin?	Smoker?	Age (years)?	Cell viability	Cell attachment/ adhesion	Cell proliferation	Cytokine production			
Gao *et al.* (2013)	HGEC	Primary	Healthy gingival tissues, healthy individuals	Not specified	Not specified	X				7	University of Louisville; RJ Reynolds Tobacco	USA
Giannopoulou *et al.* (1999)	HPDLC	Primary	Orthodontic premolar extractions; Caucasian males	Not specified	Not specified		X	X		6	P. Baehni provided equipment	Switzerland
Ho & Chang (2006)	HGF	Primary	Crown lengthening surgery, healthy individuals, no local inflammation	Not specified	Not specified	X				8	No details provided	China
James *et al.* (1999)	HPDLC	Primary	Orthodontic premolar extractions	Not specified	Not specified		X			8	Oral & Dental Research Trust; Nuffield Health Foundation	UK
Johnson & Organ (1997)	HGEC	Primary	Crown lengthening surgery, 4 female;	Non-smokers	41 (mean)	X		X	X	9	NIDR grant	USA

Study	Cell types investigated	Cell Origin				Investigations completed				Quality assessment score	Funding source	First author location
		Primary cells or cell line?	Location or origin?	Smoker?	Age (years)?	Cell viability	Cell attachment/ adhesion	Cell proliferation	Cytokine production			
			3 male, no signs of periodontitis, no systemic conditions requiring NSAIDs or antibiotics in previous 3 months									
Johnson *et al.* (2010)	HGEC	Primary	Crown lengthening surgery, healthy individuals, no systemic conditions requiring NSAIDs or antibiotics in previous 3 months	Non-smokers	< 50	X			X	8	National Institute of Dental and Craniofacial Research USA. (R29DEO10153; RO1DE13334)	USA
Kang *et al.* (2011)	HGF	Cell line	ATCC, HGF-1, gingivial biopsy from Caucasian	Not specified	28 (original source of HGF)	X				8	"None"	South Korea

Study	Cell types investigated	Cell Origin				Investigations completed				Quality assessment score	Funding source	First author location
		Primary cells or cell line?	Location or origin?	Smoker?	Age (years)?	Cell viability	Cell attachment/ adhesion	Cell proliferation	Cytokine production			
			male, "normal" health status									
Kashiwagi *et al.* (2012)	HGEC	Primary	Periodontal surgery, healthy individuals	Non-smokers	45 (mean)	X			X	9	Japan Society for the Promotion of Science	Japan
Kim *et al.* (2012)	HPDLC	Cell line	Transformed (immortalised) PDL cell line from Hiroshima University, Japan	Not specified	Not specified	X			X	8	Korea Healthcare Technology R&D Project, Ministry for Health, Welfare & Family Affairs, Korea. (A100093)	South Korea
Lee *et al.* (2005)	HGEC	Cell line	Transformed (immortalised) HGEC line from Kagoshima University, Japan	Not specified	Not specified	X		X		8	Wonkwang University	South Korea
Lee *et al.* (2008)	HGEC	Cell line	Transformed (immortalised) HGEC line from	Not specified	Not specified	X				8	Wonkwang University	South Korea

Study	Cell types investigated	Cell Origin				Investigations completed				Quality assessment score	Funding source	First author location
		Primary cells or cell line?	Location or origin?	Smoker?	Age (years)?	Cell viability	Cell attachment/ adhesion	Cell proliferation	Cytokine production			
			Kagoshima University, Japan									
Lee *et al.* (2009)	HPDLC	Cell line	Transformed (immortalised) HPDLC cell line from Wongkwang University, Japan	Not specified	Not specified	X				8	Korea Research Foundation	South Korea
Lee *et al.* (2013)	HPDLC	Primary	Orthodontic premolar extractions	Not specified	Not specified	X				7	Kyung Hee University grant	South Korea
Mahanonda *et al.* (2009)	HGEC	Primary	Crown lengthening surgery, healthy periodontium from lifetime non-smokers with no history of periodontitis	Non-smokers	Not specified	X			X	9	Thai Health Grant, Chulalongkorn University Fund, Thai Government Research Budget	Thailand
Nakao *et al.* (2009)	HGF	Primary	Gingival biopsy of healthy interdental papilla	Not specified	Not specified	X			X	9	Japan Society for the Promotion of Science	Japan

Study	Cell types investigated	Cell Origin				Investigations completed				Quality assessment score	Funding source	First author location
		Primary cells or cell line?	Location or origin?	Smoker?	Age (years)?	Cell viability	Cell attachment/ adhesion	Cell proliferation	Cytokine production			
			prior to orthodontic premolar extraction									
Nakata *et al.* (2013)	HGEC	Cell line	Cell Research Corp, Singapore, hOMK107 – from Caucasian female	Not specified	52 (original source of HGEC)	X				9	Ministry of Education, Culture, Sports, Science and Technology of Japan	Japan
Olson *et al.* (2005)	HPDLC	Cell line	Originated from periodontally and systematically healthy subjects	Not specified	Not specified			X	X	8	No details provided	USA
Park *et al.* (2013)	HGF	Cell line	Transformed (immortalised) HGF line originated from interdental papilla gingival tissue adjacent to sound premolar & permanent molar	Not specified	Not specified	X				9	Korea Healthcare Technology R&D Project of Ministry for Health, Welfare and Family Affairs, Korea; National Research Foundation of Korea.	South Korea

Study	Cell types investigated	Cell Origin				Investigations completed				Quality assessment score	Funding source	First author location
		Primary cells or cell line?	Location or origin?	Smoker?	Age (years)?	Cell viability	Cell attachment/ adhesion	Cell proliferation	Cytokine production			
			teeth in healthy subjects									
San Miguel *et al.* (2010)	HGF + HPDLC	Primary	Gingival tissues and extracted teeth ("because of clinical necessity"), healthy individuals	Non-smokers	Not specified	X				9	Texas A & M Research Foundation grant 480191; PerioSciences LLC assisted obtaining grant support.	USA
San Miguel *et al.* (2012)	HGF + HPDLC	Primary	Premolar extractions (ligament cells, adjacent healthy gingiva or interdental papilla), healthy individuals	Non-smokers	Not specified	X		X		9	PerioSciences LLC	USA
Silva *et al.* (2012)	HGF	Primary	Retromolar gingiva harvested during third molar extraction,	Non-smoker	Not specified	X				9	Chilean Fund for Science and Technology (1090142)	Chile

Study	Cell types investigated	Cell Origin				Investigations completed				Quality assessment score	Funding source	First author location
		Primary cells or cell line?	Location or origin?	Smoker?	Age (years)?	Cell viability	Cell attachment/ adhesion	Cell proliferation	Cytokine production			
			healthy female individual, no history of inflammation at site, no relevant medical or drug history in previous 6 months									
Tanur *et al.* (2000)	HGF	Not specified	Frozen cells from Eisenhower Army Medical Centre, Augusta, Georgia	Not specified	Not specified		X			7	Texas A&M University, Baylor College of Dentistry	USA
Takeuchi *et al.* (2010)	HGF + HPDLC	Primary	Gingiva harvested during impacted third molar extraction, ligament from lower premolar orthodontic extractions, "Normal" tissues	Not specified	23 - 34	X				9	Ministry of Education, Science, and Culture, Japan (20592437, 19109008, 19592142)	Japan

Study	Cell types investigated	Cell Origin				Investigations completed				Quality assessment score	Funding source	First author location
		Primary cells or cell line?	Location or origin?	Smoker?	Age (years)?	Cell viability	Cell attachment/ adhesion	Cell proliferation	Cytokine production			
			from male and female donors									
Takeuchi-Igarashi *et al.* (2014)	HGF + HPDLC	Primary	Gingiva harvested during impacted third molar extraction, ligament from lower premolar orthodontic extractions, "Normal" tissues from male and female donors	Not specified	23 - 34				X	9	Ministry of Education, Science, and Culture, Japan (20592437)	Japan
Tipton & Dabbous (1995)	HGF	Primary	Non-inflamed gingival tissues, healthy individual	Not specified	Not specified	X		X	X	9	University of Tennessee College of Dentistry	USA
Wendell and Stein (2001)	HGF	Primary	Periodontal surgery in cases of chronic periodontitis, male and female,	Not specified	35 - 65	X			X	8	National Institute of Dental and Craniofacial Research	USA

Study	Cell types investigated	Cell Origin				Investigations completed				Quality assessment score	Funding source	First author location
		Primary cells or cell line?	Location or origin?	Smoker?	Age (years)?	Cell viability	Cell attachment/ adhesion	Cell proliferation	Cytokine production			
			no antibiotics or anti-inflammatory medication 6 weeks prior to harvesting								(DE07258, DE11519)	
Wu *et al.* (2013)	HPDLC	Primary	Orthodontic premolar extractions	Not specified	"young patients"				X	9	National Natural Science Foundation of China (30973315, 81170964)	China
Wu *et al.* (2014)	HPDLC	Primary	Orthodontic premolar extractions	Not specified	"child patients"				x	9	Laboratory of Endodontics of the Fourth Military Medical University; National Natural Science Foundation of China (81170964).	China
Zhou *et al.* (2007)	HGF	Primary	Crown lengthening	Non-smokers	Not specified	x			x	8	No details provided	USA

Study	Cell types investigated	Cell Origin				Investigations completed				Quality assessment score	Funding source	First author location
		Primary cells or cell line?	Location or origin?	Smoker?	Age (years)?	Cell viability	Cell attachment/ adhesion	Cell proliferation	Cytokine production			
			surgery, clinically healthy									

HGEC= Human gingival epithelial cell, HPDLC= Human periodontal ligament cell, HGF= Human gingival fibroblast, HOEC= Human oral epithelial cell, HGEC= Human gingival epithelial cell.
*Studies investigated cell proliferation indirectly using wound repopulation.
Wording in quotation marks indicates direct quote from source data.

Appendix D Supplementary Table S3: Quality assessment of included studies based on a modified CONSORT checklist.

Study	Abstract	Background	Objectives	Intervention	Outcomes	Sample size	Randomisation	Allocation concealment	Implementation	Blinding	Statistical methods	Outcomes/ estimation	Limitations	Funding	Protocol	Total (/15)
Alpar *et al.* (1998)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✗	✓	✗	✗	✗	**6**
Argentin & Cicchetti (2004)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✗	✓	✗	**8**
Chang *et al.* (2001)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✗	✓	✗	**8**
Chang *et al.* (2002)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✗	✓	✗	**8**
Checchi *et al.* (1999)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✓	✗	**9**
Ciapetti *et al.* (1999)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✗	✗	**8**
Desjardins & Grenier (2012)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✗	✓	✗	**8**
Dinos *et al.* (2015)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✗	✗	**8**
Esfahrood *et al.* (2015)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✓	✗	**9**
Fang & Svoboda (2005)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✓	✗	**9**
Gao *et al.* (2013)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✗	✗	✓	✗	**7**
Giannopoulou *et al.* (1999)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✗	✗	✗	✓	✗	**6**

Study	Abstract	Background	Objectives	Intervention	Outcomes	Sample size	Randomisation	Allocation concealment	Implementation	Blinding	Statistical methods	Outcomes/ estimation	Limitations	Funding	Protocol	Total (/15)
Ho & Chang (2006)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✗	✗	**8**
James *et al.* (1999)	✓	✓	✓	✗	✓	✗	✗	✗	✗	✗	✓	✓	✓	✓	✗	**8**
Johnson & Organ (1997)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✓	✗	**9**
Johnson *et al.* (2010)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✗	✓	✗	**8**
Kang *et al.* (2011)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✗	✓	✗	**8**
Kashiwagi *et al.* (2012)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✓	✗	**9**
Kim *et al.* (2012)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✗	✓	✗	**8**
Lee *et al.* (2005)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✗	✓	✓	✓	✗	**8**
Lee *et al.* (2008)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✗	✓	✗	**8**
Lee *et al.* (2009)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✗	✓	✗	**8**
Lee *et al.* (2013)	✗	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✗	✓	✗	**7**
Mahanonda *et al.* (2009)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✓	✗	**9**
Nakao *et al.* (2009)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✓	✗	**9**

Study	Abstract	Background	Objectives	Intervention	Outcomes	Sample size	Randomisation	Allocation concealment	Implementation	Blinding	Statistical methods	Outcomes/ estimation	Limitations	Funding	Protocol	Total (/15)
Nakata *et al.* (2013)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✓	✗	**9**
Olson *et al.* (2005)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✗	✗	**8**
Park *et al.* (2013)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✓	✗	**9**
San Miguel *et al.* (2010)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✓	✗	**9**
San Miguel *et al.* (2012)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✓	✗	**9**
Silva *et al.* (2012)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✓	✗	**9**
Tanur *et al.* (2000)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✗	✗	✓	✗	**7**
Takeuchi *et al.* (2010)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✓	✗	**9**
Takeuchi-Igarashi *et al.* (2014)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✓	✗	**9**
Tipton & Dabbous (1995)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✓	✗	**9**
Wendell and Stein (2001)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✗	✓	✗	**8**
Wu *et al.* (2013)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✓	✗	**9**
Wu *et al.* (2014)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✓	✗	**9**

Study	Abstract	Background	Objectives	Intervention	Outcomes	Sample size	Randomisation	Allocation concealment	Implementation	Blinding	Statistical methods	Outcomes/ estimation	Limitations	Funding	Protocol	Total (/15)
Zhou *et al.* (2007)	✓	✓	✓	✓	✓	✗	✗	✗	✗	✗	✓	✓	✓	✗	✗	**8**

Appendix E Supplementary Table S4: Principal findings of studies which investigated cell viability, cell attachment or adhesion, cell proliferation or wound repopulation.

Study	Cell types investigated	Assay used?	Principal finding
Cell viability			
Alpar *et al.* (1998)	HPDLC + HGF	Fluorescent dyes and trypan blue exclusion test	Reversible effects with 1.9-10.3 mM (24 h, vacuolation, impaired membrane integrity, no p value presented, both HPDLC & HGF) Irreversible toxicity with 10.3-15.5 mM (≥24 h, no p value presented) ED_{50} = 15.19-15.56 mM depending on cell type and assay (24 h)
Argentin & Cicchetti (2004)	HGF	Trypan blue exclusion test	Reduction with 10 µM (24 h, $p<0.01$, >25% reduction); approx. 60% reduction with 1 mM (24 h, $p<0.001$)
Chang *et al.* (2001)	HPDLC	MTT	No effect observed with 5 mM (4 h) At 5-20 mM cytotoxicity observed in concentration- and time-dependent manner (6, 24 h; no p value presented)
Chang *et al.* (2002)	HPDLC	MTT	Reduced viability with 5, 10, 15 mM (24 h, $p<0.05$); reduction >70% with 20, 25 mM (24 h, $p<0.001$)
Checchi *et al.* (1999)	HGF	Neutral red uptake assay	Reduced viability with 3.7 mM* (48 h, $p<0.05$), no effect seen at 24 h Stimulatory effect with 370 µM* (24 & 48 h) for cells from ≥40 y ($p<0.05$, NS at 48 h for smokers)
Ciapetti *et al.* (1999)	HGF	Neutral red uptake assay	No effect of 37 µM* (24, 48 h; $p<0.05$) Stimulatory effect with 370 µM* (24 & 48 h, non-smokers only, $p<0.05$) Reduced viability with 3.7 mM* (24 h, non-smokers only, $p<0.05$, approx.10% reduction); smokers and non-smokers reduced by approx. 40% at 48 h ($p<0.05$)
Desjardins & Grenier (2012)	HGF + HOEC	MTT	Reduced viability with 310-920 µM* (24 h, $p<0.005$, both HGF & HOEC)
Dinos *et al.* (2015)	HGF	Microscopic observation	Cytotoxicity observed with 4 mM nicotine (4 d, no statistical testing presented)

Study	Cell types investigated	Assay used?	Principal finding
Esfahrood *et al.* (2015)	HGF	MTT	No effect of 1 nM – 0.1 mM (24 h) Reduced viability with 1 mM – 20 mM (24 h, $p<0.05$)
Gao *et al.* (2013)	HGEC	SRB	No significant difference with 6.2 μM-2.8 mM* (48 h) Stimulatory effect of 460 μM* (5 h, no p value presented, approx. 50% increase) EC-50 not reached with <2.8 mM* (24 h)
Ho & Chang (2006)	HGF	Lactate dehydrogenase leakage	Reduced viability with 5, 10, 15, 20 mM (24 h, $p<0.05$, approx. 30/45/65/90% reduction respectively)
Johnson & Organ (1997)	HGEC	MTS	No effect with 100 nM, 10 μM or 1 mM (4 & 24 & 48 h)
Johnson *et al.* (2010)	HGEC	MTS	No effect with 100 nM & 1 mM (24 h, no data shown)
Kang *et al.* (2011)	HGF	MTT	Reduced viability with 1, 5, 10, 20 mM (24 h, $p<0.05$, approx. 30/50/80/90% reduction respectively)
Kashiwagi *et al.* (2012)	HGEC	"Preliminary experiments"	No effect of 10 nM – 1 mM (24 h)
Kim *et al.* (2012)	HPDLC	MTT	Reduced viability with 10 mM (24 h, $p<0.05$, approx. 45% reduction) No effect with 1, 5 mM (24 h, $p<0.05$)
Lee *et al.* (2005)	HGEC	MTT	Reduced viability with 6, 60, 300, 600 μM (24-120 h, $p<0.05$, approx. 30/50/55/75% reduction respectively at 24 h) IC_{50}= 300 μM (24 h)
Lee *et al.* (2008)	HGEC	MTT	Reduced viability with 5 mM (8 h, $p<0.05$, approx. 40% reduction), 20 mM (4 h, $p<0.05$, approx. 45% reduction)

Study	Cell types investigated	Assay used?	Principal finding
Lee *et al.* (2009)	HPDLC	MTT	Reduced viability with 10, 15 mM (24 h, $p<0.05$, approx. 20/60% reduction respectively); 10mM showed effects after 9 h ($p<0.05$)
Lee *et al.* (2013)	HPDLC	MTT	Reduced viability with 10 mM (12 h, $p<0.05$, approx. 25% reduction); reduced viability with 5, 10 mM (24 h, $p<0.05$, approx. 20/40% reduction respectively); reduced viability with 5, 10 mM (48 & 72 h, $p<0.05$, approx. 40/60% reduction respectively); no effect with 2mM (12, 24, 48, 72 h)
Mahanonda *et al.* (2009)	HGEC	MTT and trypan blue exclusion	No effect with 0.1, 0.3, 1mM (24 h)
Nakao *et al.* (2009)	HGF	"Preliminary experiments"	No effect up to 10 mM (no duration provided [24 h implied])
Nakata *et al.* (2013)	HGEC	MTT	No effect with 1 µM & 1 mM (24 h)
Park *et al.* (2013)	HGF	MTT	No significant effect of 5 mM nicotine (24 h)
San Miguel *et al.* (2010)	HGF + HPDLC	MTS	Reduced viability with 6, 8, 10 mM (10 h, no p value presented, approx. 40-50% reduction, both HGF & HPDLC)
San Miguel *et al.* (2012)	HGF + HPDLC	MTS	HGF: Reduced viability 6 & 8 mM (30 m, $p<0.05$, approx. 40% reduction) HPDLC: Reduced viability with 6 & 8 mM (60 m, $p<0.05$, approx. 20-25% reduction)
Silva *et al.* (2012)	HGF	MTS	No effect with 150 nM* - 200 µM* (24, 48, 72 h; $p<0.05$)
Takeuchi *et al.* (2010)	HGF + HPDLC	Trypan blue exclusion test	Stimulatory effect with 620 nM* (12-48 h, $p<0.05$, both HGF & HPDLC) Reduced viability with 6.2 & 62µM* (12-48 h, $p<0.05$, approx.40-50%/ 90-100% reduction respectively, both HGF & HPDLC)
Tipton & Dabbous (1995)	HGF	Microscopic observations during "Preliminary experiments".	Reduced viability with >5 mM* (24 h, no duration or p value stated)

Study	Cell types investigated	Assay used?	Principal finding
Wendell and Stein (2001)	HGF	Trypan blue exclusion test	No effect with 1 nM, 1 µM, 1 mM (12-48h)
Zhou *et al.* (2007)	HGF	MTT	No effect with 1.54 mM* (72 h)
Cell attachment or adhesion			
Esfahrood *et al.* (2015)	HGF	MTT	Reduced adhesion with 1 nM, 1 µM, 1 mM, 5 mM (24 h, $p<0.05$, root surface)
Giannopoulou *et al.* (1999)	HPDLC	Cell count	Reduced attachment with 150 nM* (6 h, no p values presented, plastic culture plates, dose dependant inhibition 0.6-15.4 µM*)
James *et al.* (1999)	HPDLC	MTT	Reduced attachment with 31 mM* (24 h, $p<0.05$, plastic culture plates, greater effect for cells from lower passages)
Tanur *et al.* (2000)	HGF	Cell count	Root surface: Reduced cell attachment with 150, 310, 620 nM* (4 w, $p<0.05$) Glass surface: Reduced cell attachment with 310, 620 nM* (4 w, $p<0.05$)
Cell proliferation			
Alpar *et al.* (1998)	HPDLC + HGF	Cell count using trypan blue, SRB, DNA content	Reduced proliferation with >3.9 mM and complete arrest of proliferation with >31 mM (24 h, both cell types, no p value presented)
Argentin & Cicchetti (2004)	HGF	Cell count using Neubauer Chamber and trypan blue	No effect with 1 µM (24, 36, 48,72 h)
Chang *et al.* (2002)	HPDLC	Thymidine incorporation	Reduced proliferation with 25, 50, 100, 200 µM (96 h, $p<0.05$, approx. 20/50/70/85% reduction respectively) Complete arrest of proliferation with 400 µM (96 h, $p<0.001$)
Checchi *et al.* (1999)	HGF	Flow cytometry using Hoechst 33342	Reduced proliferation with 3.7 mM* (24 h, $p<0.05$, no effect on cells from smokers aged >40 y) No effect with 37µM* or 370 µM* (24 h, $p<0.05$)

Study	Cell types investigated	Assay used?	Principal finding
Ciapetti *et al.* (1999)	HGF	Hoechst DNA quantitation	Reduced proliferation with 3.7 mM* (48 h, $p<0.05$) No effect with 37 μM*, 370 μM*(24, 48 h, $p<0.05$) or 3.7 mM* (24 h, $p<0.05$)
Giannopoulou *et al.* (1999)	HPDLC	Thymidine incorporation	Reduced proliferation with 0.6, 1.5, 3, 6, 12 μM* (24-48 h, no p value presented, approx. 25/40/50/80/90% reduction respectively) No effect with 30, 150 nM* (24-48 h)
Johnson & Organ (1997)	HGEC	Acid Phosphatase assay	No effect with 100 nM, 10 μM or 1 mM (4-48 h)
Lee *et al.* (2005)	HGEC	Flow cytometry + Western Blot for cell-cycle regulatory protein	Implied decrease in cell proliferation, with more cells in G0 or G1 phase and fewer in S phase of the cell cycle Increase in p21 and decrease in p53 expression with 6, 60, 300 μM
Olson *et al.* (2005)	HPDLC	Cell count using Coulter counter	Increase in proliferation of cells when exposed to 2.3 mM (24 h, $p<0.05$) Reduction in proliferation of cells when exposed to 9.2mM (24 h, $p<0.05$)
San Miguel *et al.* (2012)	HGF + HPDLC	Bromodeoxyuridine assay	HGF: Reduced proliferation with 6, 8 mM (30 m, $p<0.05$, approx. 20% reduction) HPDLC: No effect with 6, 8 mM (30 m)
Tipton & Dabbous (1995)	HGF	Thymidine incorporation	Reduced proliferation with 62 μM* or 0.2, 0.3, 0.5, 0.6, 1.5, 3.1 or 4.6mM* (24 h, $p<0.05$)
Wound repopulation (or rate of artificial wound closure)			
Dinos *et al.* (2015)	HGF	Photomicrography	No effect with 1, 2, 4 mM (24, 48 h; $p<0.05$) Reduced wound repopulation with 4mM (96 h, $p<0.05$) Reduced wound repopulation with 1, 2, 4 mM (144 h, $p\leq0.001$)
Fang & Svoboda (2005)	HGF	Photomicrography	Reduced wound closure rates with 0.5 μM (12, 24, 36 h; $p<0.05$)

HGEC= Human gingival epithelial cell, HPDLC= Human periodontal ligament cell, HGF= Human gingival fibroblast, HOEC= Human oral epithelial cell, HGEC= Human gingival epithelial cell, h= hour(s), d= day(s).

Appendix F Supplementary Table S5: Principal findings of studies which investigated inflammatory mediator production.

Study	Cell types investigated	Inflammatory mediator assessed	Principal finding
Desjardins & Grenier (2012)	HGF + HOEC	CCL5, IL-6, IL-8	HOEC: increase of CCL5 with 300 nM* (24 h, $p \leq 0.005$, no effect on IL-6 + IL-8) HGF: no effect on CCL5, IL-6, Il-8 with 300 nM* (24 h, data not shown)
Johnson & Organ (1997)	HGEC	PGE_2, IL-1α, IL-1β	No effect on PGE_2 with 100 nM, 10 µM, 1 mM (4-48 h) Increased IL-1α in cell lysate with 1mM (24, 48 h; $p=0.0061$, no effect seen in cell culture supernatant) No effect on IL-1β in cell lysate with 1mM (4, 24, 48 h; $p<0.01$)
Johnson *et al.* (2010)	HGEC	IL-1α, IL-8	Increase in IL-1α with 1 mM (24h, $p<0.0018$, no effect with 0.1 µM) No effect on IL-8 at 100 nM, 1 mM (24 h)
Kashiwagi *et al.* (2012)	HGEC	IL-8	Increased production with 1 mM (24 h, $p<0.01$, HGEC stimulated with IL-1β)
Kim *et al.* (2012)	HPDLC	MMP-2, MMP-9, PGE_2	Increased PGE_2 with 5, 10 mM (24 h, $p<0.05$) Increased MMP-2 + MMP-9 with 1, 5, 10 mM (24 h, no p value presented)
Mahanonda *et al.* (2009)	HGEC	IL-8	Increased IL-8 with 0.3, 1 mM (24 h, $p<0.05$, HGEC stimulated with P.*gingivalis* LPS + TNF-α)
Nakao *et al.* (2009)	HGF	PGE_2	Increased PGE_2 with 1-10 mM (6 h, no p value presented)
Olson *et al.* (2005)	HPDLC	IL-6	Increased IL-6 with 1.5, 2.3 mM* (24 h, $p<0.05$) Decreased IL-6 with 9.24 mM* (24 h, $p<0.05$)
Takeuchi-Igarashi *et al.* (2014)	HGF + HPDLC	TGF-β1, MMP-1, TIMP-1	HGF: increased in TGF-β1 in cell culture supernatant with 6.2 nM* (12, 24 h; $p<0.05$, no effect seen in cell lysate); increase in MMP-1 in cell lysate with 6.2 nM* (24, 48 h, not statistically significant); increase in TIMP-1 with 6.2 nM* (12, 24, 48 h; $p<0.05$). HPDLC: increased TGF-β1 in cell lysate with 6.2 nM* (12 h, $p<0.01$);); increase in MMP-1 in cell lysate (24, 48 h; not statistically significant); increase in TIMP-1 with 6.2 nM* (12, 24, 48 h; $p<0.05$).

Study	Cell types investigated	Inflammatory mediator assessed	Principal finding
Tipton & Dabbous (1995)	HGF	Collagenase activity	Increased collagenase activity with 1.5, 3.1, 4.6 mM* (144 h, $p<0.008$)
Wendell and Stein (2001)	HGF	IL-6 & IL-8	Increase in IL-6 with 1 nM, 1 μM, 1 mM (48 h, p=0.018/0.003/0.024 respectively); 1nM induced the greatest response at 24 h (p=0.02) Increase in IL-8 with 1 nM (24 h, $p<0.02$, no effect at 48 hrs)
Wu *et al.* (2013)	HPDLC	IL-1β	Increase in secretion with 10μM (72 h, $p<0.01$)
Wu *et al.* (2014)	HPDLC	IL-1β + IL-8	Increased secretion of IL- 1β + IL-8 with nicotine 10μM (24 h, $p<0.01$)
Zhou *et al.* (2007)	HGF	MMP-1, MMP-2, MMP-3, MMP-14, TIMP-1, TIMP-2	No effect on MMP-1 and MMP-2 with 1.5 mM* (48 h) Increased prevalence in membrane extracts of MMP-14 (43 kDa) and MMP-2 (68kDa) with 1.5 mM* (48 h, no p value presented) Slightly reduced levels of TIMP-1 in nicotine-treated cells (1.54 mM, 48 h, no p values presented); TIMP-2 appeared to be redistributed to cell membranes by nicotine exposure

HGEC= Human gingival epithelial cell, HPDLC= Human periodontal ligament cell, HGF= Human gingival fibroblast, HOEC= Human oral epithelial cell, HGEC= Human gingival epithelial cell, h= hour(s), d= day(s), MMP= Matrix Metalloproteinase, TIMP= Tissue Inhibitors of Metalloproteinases.

Appendix G CONSORT checklist for pilot and feasibility trials

Section/Topic	Item No	Checklist item	Reported in section No.
Title and abstract			
	1a	Identification as a pilot or feasibility randomised trial in the title	3.1
	1b	Structured summary of pilot trial design, methods, results, and conclusions (for specific guidance see CONSORT abstract extension for pilot trials)	3.1
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale for future definitive trial, and reasons for randomised pilot trial	3.2
	2b	Specific objectives or research questions for pilot trial	3.3.1, 3.3.2
Methods			
Trial design	3a	Description of pilot trial design (such as parallel, factorial) including allocation ratio	3.4.1
	3b	Important changes to methods after pilot trial commencement (such as eligibility criteria), with reasons	3.4.17, Table 3.12
Participants	4a	Eligibility criteria for participants	3.4.2
	4b	Settings and locations where the data were collected	3.4.2

Section/Topic	Item No	Checklist item	Reported in section No.
	4c	How participants were identified and consented	3.4.3
Interventions	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered	3.4.5, 3.4.6, 3.4.7
Outcomes	6a	Completely defined prespecified assessments or measurements to address each pilot trial objective specified in 2b, including how and when they were assessed	3.4.12, 3.4.15
	6b	Any changes to pilot trial assessments or measurements after the pilot trial commenced, with reasons	3.4.17
	6c	If applicable, prespecified criteria used to judge whether, or how, to proceed with future definitive trial	NA
Sample size	7a	Rationale for numbers in the pilot trial	3.4.4
	7b	When applicable, explanation of any interim analyses and stopping guidelines	NA
Randomisation:			
Sequence generation	8a	Method used to generate the random allocation sequence	3.4.9
	8b	Type of randomisation(s); details of any restriction (such as blocking and block size)	3.4.9
Allocation	9	Mechanism used to implement the random allocation sequence (such as sequentially numbered containers), describing any steps taken to conceal the sequence until interventions were assigned	3.4.11

Section/Topic	Item No	Checklist item	Reported in section No.
concealment mechanism			
Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions	3.4.9
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how	3.4.11
	11b	If relevant, description of the similarity of interventions	NA
Statistical methods	12	Methods used to address each pilot trial objective whether qualitative or quantitative	3.4.21
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were approached and/or assessed for eligibility, randomly assigned, received intended treatment, and were assessed for each objective	3.5.2, Table 3.13, Figure 3.5, Table 3.14, Table 3.40

Section/Topic	Item No	Checklist item	Reported in section No.
	13b	For each group, losses and exclusions after randomisation, together with reasons	3.5.4, Table 3.15, Table 3.16
Recruitment	14a	Dates defining the periods of recruitment and follow-up	3.5.2
	14b	Why the pilot trial ended or was stopped	NA
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group	3.5.5, Table 3.17, Table 3.18, Table 3.19
Numbers analysed	16	For each objective, number of participants (denominator) included in each analysis. If relevant, these numbers should be by randomised group	3.5
Outcomes and estimation	17	For each objective, results including expressions of uncertainty (such as 95% confidence interval) for any estimates. If relevant, these results should be by randomised group	3.5.12, 3.5.14
Ancillary analyses	18	Results of any other analyses performed that could be used to inform the future definitive trial	Chapter 4 & 5

Section/Topic	Item No	Checklist item	Reported in section No.
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	3.5.6
	19a	If relevant, other important unintended consequences	NA
Discussion			
Limitations	20	Pilot trial limitations, addressing sources of potential bias and remaining uncertainty about feasibility	3.6.3
Generalisability	21	Generalisability (applicability) of pilot trial methods and findings to future definitive trial and other studies	3.6.2
Interpretation	22	Interpretation consistent with pilot trial objectives and findings, balancing potential benefits and harms, and considering other relevant evidence	3.6.2
	22a	Implications for progression from pilot to future definitive trial, including any proposed amendments	3.6.4
Other information			
Registration	23	Registration number for pilot trial and name of trial registry	3.4.18
Protocol	24	Where the pilot trial protocol can be accessed, if available	3.4.18
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	3.4.18
	26	Ethical approval or approval by research review committee, confirmed with reference number	3.4.17

Appendix H Participant Information Sheet (PIS)

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Newcastle University

Participant Information Sheet

Study of Electronic Cigarettes to Help Smokers with Periodontitis Stop Smoking

We invite you to take part in a research study.

- Before you decide whether to take part, it is important for you to understand why the research is being done and what it will involve.
- Please take time to read the following information carefully. Discuss it with friends and relatives if you wish.
- You are free to decide whether or not to take part in this trial. If you choose not to take part, this will not affect the care you get from your own doctor or dentist.
- Ask us if there is anything that is not clear or if you would like more information.

Important things you need to know

- We want to find out if electronic cigarettes (e-cigarettes) can help smokers (who have periodontitis) stop smoking.
- The study will have two groups: one will receive normal advice from the dentist and the other will receive the same advice but also be provided with an e-cigarette starter kit.
- Normal periodontal treatment will be provided as part of the study. On top of normal care, there will be 1-3 additional study visits.
- You do not have to pay for the e-cigarette but you will have to buy any future e-liquid you need.
- You can stop taking part in the study at any time.

Contents

How to contact us

If you have any questions about this study, please talk to the researchers who organise it: Dr Holliday or Professor Preshaw on 0191 202 6812

Summary

Why?

Smoking is known to be bad for your health and is particularly bad for your periodontium (gums). Dentists have a role to play in helping their patients to stop smoking. E-cigarettes are the most recent method people are using to help them stop smoking. This study aims to start finding out if e-cigarettes can be useful to help people to stop smoking and to see if their periodontal health improves.

What?

- This study is looking at patients who have periodontitis that is classed as '*severe*' and '*chronic*'.
- All participants will receive usual stop smoking advice from their dentist. Half of the participants will also be provided with an e-cigarette starter kit.
- Participants in this study will have to attend 7 study visits. These visits will include normal periodontal therapies as well as measurements for the study. A small number of participants will be asked to attend 1-3 additional visits to provide more detailed feedback on their experience.
- Participants who take part in this study will have periodontal therapies to improve their oral health and will be helping us understand the science behind e-cigarettes so we can inform future patients.

Who?

Those who have a diagnosis of severe chronic periodontitis and smoke (over 10 factory-made cigarettes/day or 7g [0.25oz] loose tobacco/day or 14 hand-rolled cigarettes/day) can enter this study.

Where?

The study visits will be conducted within the Dental Clinical Research Facility of the Newcastle Dental Hospital.

How, when?

The study lasts for 6-7 months once you agree to take part.

More details

Study details

Full title: A mixed methods feasibility study of electronic cigarette use by patients with periodontitis.

Short title: Feasibility study of e-cigarettes in periodontitis.

R+D study identification number: 7938

Researchers: Dr Richard Holliday, Professor Philip Preshaw, Professor Elaine McColl, Professor Falko Sniehotta and Ms Vicky Ryan.

Location: Dental Clinical Research Facility, Newcastle Upon Tyne NHS Foundation Trust.

Protocol version: 1.0 (30/07/2016)

Invitation

We would like to invite you to take part in our research study. Joining the study is entirely up to you, before you decide we would like you to understand why the research is being done and what it would involve for you. One of our team will go through this information sheet with you, to help you decide whether or not you would like to take part and answer any questions you may have.

We'd suggest this should take about 20 minutes. Please feel free to talk to others about the study if you wish.

The first part of the Participant Information Sheet tells you the purpose of the study and what will happen to you if you take part.

Ask us if there is anything that is not clear.

A bit of background information

Smoking is still common with around 1 in 5 adults smoking in the UK. Smokers can find it very hard to stop smoking.

Smoking causes many health problems such as heart and lung problems and increased risks of cancer. Smoking also causes oral health problems such more severe gum disease and increased rates of tooth loss.

Currents techniques for helping smokers to stop smoking do not typically address the behaviours and sensations associated with the act of smoking (e.g. handling a cigarette, inhaling, taste, feel of smoke in mouth).

E-cigarettes are battery-operated devices that attempt to mimic the act of smoking and thus provide these effects. E-cigarettes have been shown to be a useful aid in stopping people smoking. No research has been completed before within the dental setting.

What is the purpose of the study?

The main purpose of this study is to expand our knowledge of how e-cigarettes could be used to help patients with severe chronic periodontitis stop smoking. We will also be investigating any good or bad effects seen in the mouth.

This study is also being undertaken for educational purposes.

Why have I been invited?

You have been identified as having periodontitis and also being a smoker. We are inviting 80 patients to participate in the study.

Do I have to take part?

No. It is up to you to decide to join the study. We will describe the study and go through this information sheet. If you agree to take part, we will then ask you to sign a consent form. You are free to withdraw at any time, without giving a reason. This would not affect the standard of care you receive.

What will happen to me if I take part?

This study involves 7 study visits. The details of these visits are as follows:

Pre-study visit

This visit will involve an examination of your mouth to check that your oral health is suitable for this research study.
We will describe the study and go through this information sheet. You will then have the opportunity to ask any questions.

Visit 1

At the start of this visit we will ask you to sign a consent form to show that you have agreed to take part. This visit will involve collection of a range of measurements from within the mouth. Samples will be collected of your saliva and the liquid that sits around the edges of your teeth. We will ask you questions about smoking, mood, health and lifestyle. We will measure the amount of Carbon Monoxide (CO) in your breath (this shows how much smoke you inhale).
During the visit the dentist will discuss with you stopping smoking. You will either receive usual care which involves a discussion with the dentist or, as well as discussion, you will receive an e-cigarette starter kit. You will be provided some training on how to use the device.

Visit 2

You will be asked to try to stop smoking after this session. During this session usual periodontal therapies will be provided to all participants. This involves detailed deep 'cleaning' of the teeth under local anaesthetic. Half of the mouth will be cleaned on this visit.

Visit 3

The remaining half of the mouth will be treated on this visit.

Visit 4

During this visit the dentist will check your mouth and provide further advice on home cleaning. Some measurements will be collected during this visit.

Visit 5

During this visit the dentist will check your mouth and provide further advice on home cleaning. All the baseline measurements will be repeated at this visit.

Visit 6

During this visit the dentist will check your mouth and provide further advice on home cleaning. All the baseline measurements will be repeated at this visit.

Additional study visits:

Interviews

Fourty participants will be invited to attend for extra interviews with the researchers. There will be two interviews around study visits 4 and 6. Each interview will last for around 60 minutes.

Focus group

Ten participants will be asked to attend for a focus group. This will involve a single visit and will last for around 90 minutes.

What will I have to do?

If you agree to take part you will be required to attend the study visits as described above. You will also be asked to complete a weekly diary of your smoking/e-cigarette use which can be completed on your smart phone or on paper.

How will you decide what group I go in?

You will be randomly allocated to one of two groups, similar to tossing a coin. One group will receive normal stop smoking advice. One group will receive normal stop smoking advice and will also be provided with an e-cigarette starter kit. You are just as likely to be allocated to either group.

Some of the researchers in the study will not know what group you are in. You will be asked not to tell them what group you are in. The research nurse will remind you of this before each relevant study visit.

What happens if I don't get an e-cigarette?

Half of the participants in this study will not be given an e-cigarette. This is important for our research results. If you end up in this group you will be given normal advice and have the option of being referred to see a specialist stop smoking practitioner.
We understand that this may be disappointing but we would ask that you refrain from using an e-cigarette during the study, especially for the first four weeks. If you are still smoking at the end of the study you will be free to use an e-cigarette at this point to help you stop smoking.

What happens if I get an e-cigarette?

Half of the participants in this study will be given an e-cigarette starter pack. This includes a small volume of e-liquid that will last you for around 2-4 weeks. You will need to buy your own refills of the e-liquid after this point. We will provide you with information about where you can buy this. With average usage you can expect to spend around £5-£10 a week on e-liquid/ (2016 costs).

The e-cigarette also contains a 'clearomizer' which needs to be replaced every 2-4 weeks. These cost £4.99 (2016 costs).

What happens if I can't stop smoking?

We understand that not everyone will be able to stop smoking. This is perfectly fine and it is really important that you keep attending for all the study visits even if you have not stopped smoking. It is important for us to understand why you didn't manage to stop.

Media stories about e-cigarettes

E-cigarettes are a topical issue and attract lots of press attention. It is likely that during the study you will see news reports in the media (newspapers, TV). The research team constantly review the research as it is updated, with the advice of national organisations. If they felt there was a significant change, that you had to be aware of, they would inform you of this during the study.

If you have any concerns during the study please feel free to contact the research team to discuss them.

Expenses and payments?

There is no payment to take part in this study. Those invited to attend interviews or the focus group will be given £10 towards travel expenses to these visits.

What are the possible benefits of taking part?

This study will involve normal periodontal therapies and it is likely that you will see significant improvements in your gum health. We will also be supporting you to stop smoking during this study and hope that we can help you to stop or significantly reduce your tobacco intake. This will have many general and oral health benefits for you.

We do not know how good e-cigarettes are for helping patients with periodontitis stop smoking. This is one of the reasons why we are conducting the research.

Your contribution to this study will help people in the future with a similar condition.

What are the potential disadvantages and risks of taking part?

This study requires several visits, although normal periodontal therapies require a similar number of dental visits. Some of these visits (visit 1, 5 and 6) require several measurements and may last for around 1-1.5 hours.

There are normal risks associated with periodontal therapies which include discomfort, infection, tooth sensitivity and gum recession.

Using an e-cigarette, like any therapy or medication, carries some risks. However, we know e-cigarettes are significantly safer than smoking; 'e-cigarettes are around 95% less harmful than smoking' (Public Health England 2015). The most common side effects reported by e-cigarette users are mouth/throat irritation, nausea and sleep disturbances.

E-cigarettes deliver nicotine in a similar way to other forms of Nicotine Replacement Therapy [NRT] e.g. gums, patches etc. NRT is very safe and taken by many people. However, NRT is best avoided or taken with care in a small number of medical conditions and the research team will ask you about your medical history to check this.

What will happen to any samples I give?

During this study you will be asked to give saliva samples (by drooling into a cup) and the dentist/hygienist will collect very detailed samples of the saliva around your teeth/gums. These samples will be collected on 3 occasions. No blood tests will be required.

Initial preparation and analysis will be completed in the Cell and Molecular biosciences laboratory in the School of Dental Sciences, Newcastle University. Some of the tests we need to complete on the samples will be conducted by external laboratories; some in the UK and some in the United States. In the consent form we will be asking for your permission to send anonymous samples to countries outside of the European Economic Area (EEA). Additionally we will be asking for your permission to store any remaining samples for use in future projects. These samples will be anonymous and stored within an official Biobank within Newcastle University.

Audio-visual recording.

Some of the treatment visits and interviews will be audio recorded. This helps us check that everyone received the same treatment and also helps us collect the results. We may use anonymous verbatim quotation in publications. Additionally we will be taking clinical photographs of your mouth. These will be close up images of your teeth and gums. Anonymous photographs may be used in publications, if you give permission for this.

We will ask for permission to use audio recording and take clinical photographs in the consent form.

What if there is a problem?

Any complaint about the way you have been dealt with during the study or any possible harm you might suffer will be addressed.

If you have a concern about any aspect of this study, you should ask to speak to the researchers who will do their best to answer your questions [0191 2821170]. If you remain unhappy and wish to complain formally, you can do this via the NHS Complaints Procedure. Details can be obtained from the Patient Relations Department on 0191 2231382.

Normal NHS insurance is applicable to this study such as the Newcastle Upon Tyne Hospitals NHS Trust liability insurance and NHS indemnity.

In the event that something does go wrong and you are harmed during the research and this is due to someone's negligence then you may have grounds for a legal action for compensation against 'The Newcastle Upon Tyne Hospitals NHS Foundation Trust' but you may have to pay your legal costs. The normal National Health Service complaints mechanisms will still be available to you (if appropriate).

Will my taking part in the study be kept confidential?

Yes. We will follow ethical and legal practice and all information about you will be handled in confidence.

All information which is collected about you during the course of the research will be kept strictly confidential, and any information about you which leaves the hospital will have your name and address removed so that you cannot be recognised.

Study records will be kept in a locked filing cabinet with restricted access in an NHS or Newcastle University office.

The study will comply with Data Protection Act 1998 and Caldicott Principles.

The study records will be retained for 5 years before being disposed of securely.

Involvement of your Medical Doctor and Dentist?

Your medical doctor and dentist will be informed that you are taking part in this study (if you wish).

Does it matter if I'm pregnant or become pregnant?

If you are pregnant, you will not be able to take part in this study. If you fall pregnant during the study please inform the research team.

Will any genetic tests be done?

No.

What will happen to the results of the research study?

The research team will write a report which will be published in medical journals. They may also show the results at conferences they attend.

A newsletter including a summary of the study results can be sent to you if you request this.

What happens if I can't continue with the study?

In the unlikely event that you lose capacity during the period of the study the research team would retain personal data and samples collected and continue to use it confidentially for this study. As previously mentioned, any remaining samples will be stored for use in future research.

Who is organising and funding the research?

The lead researcher is Dr Richard Holliday who will be in charge of the day to day running of the study.

Funded for this study is being provided through a National Institute of Health Research Doctoral Research Fellowship Award.

Who has reviewed the study?

All research in the NHS is looked at by independent group of people, called a Research Ethics Committee, to protect your interests. This study has been reviewed and given a favourable opinion by the RES Committee North East- Tyne and Wear South Research Ethics Committee.

Further information and contact details

1. General information about research: http://www.nhs.uk/Conditions/Clinical-trials/Pages/Introduction.aspx

2. Specific information about this research project: Dr Holliday, 0191 282 1170, Richard.holliday@newcastle.ac.uk.

3. Advice as to whether you should participate. Dr Holliday will discuss any questions you have at his first visit with you.

4. Who they should approach if unhappy with the study? Dr Holliday or the NHS Complaints Procedure: 0191 223 1382 - Patient Relations Department.

Appendix I PIC proforma

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Newcastle University

Participant Identification Centre Referral Proforma

Referring dental practice?	
Potential research participant details?	Name:
	Address:
	DOB:
	Tel:
	Mobile:
	Email:

Summary inclusion and exclusion criteria

Inclusion criteria:

- **Smoker** of burnt tobacco (> 10 cigs/day)
- **Periodontitis** defined as: PPDs of ≥ 5mm at ≥ 8 sites
- Minimum of **20 natural teeth** (excluding 3rd molars)
- Age: 18+

Exclusion criteria:

- Requiring extensive dental, orthodontic or implant treatment, or treatment for peri-implantitis.
- Regular user of an e-cigarette (use on >2 days in the last 30 days)
- Received any non-surgical periodontal therapy other than a routine scale and polish in the last 6 months.
- Significant MH or pregnant.

Version 0.2 (06/02/2017)

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Newcastle University

Relevant Medical History: **Medications:**	
Previous Dental History:	
Form completed by:	Name: Signature: Role: Date:

Please return this form to:

Dr Richard Holliday, Dental Clinical Research Facility, Newcastle Dental Hospital, Richardson Road, Newcastle Upon Tyne, NE2 4AZ.

Version 0.2 (06/02/2017)

Appendix J E-cigarette users guide

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Newcastle University

How to use your e-cigarette?

A guide for new e-cigarette users.

This guide has been specifically developed for participants in this research study. It was produced in consultation with experienced vapers.

What's included?

Batteries

(2 provided)

'Tanks' or 'Clearomisers'

(2 provided)

UK plug

USB adapter

e-liquid

(2 bottles with choice of Blended Tobacco, Crisp Mint, Dark Cherry, VPure [unflavoured])

Important things you need to know

- Before you use the e-cigarette please read the manufacturers user's guide provided starter kit box (you need to pull out the polystyrene). This has important safety information.
- Only use the charger provided. NEVER use another charger.
- The date on the products refers to the date they were manufactured and not the expiry date. The manufacturer don't report an expiry date but we would recommend using a expiry date 3 years from the date of manufacturer.
- Keep the e-cigarette and e-liquid out of the reach of children at all times.
- It is recommend that you only use Vype e-liquid in this Vype eTank e-cigarette.
- The e-cigarette can be locked/ unlocked by pressing the button on the device three times

Where can I get more e-liquid from?

- The manufacturers website @ www.govype.com
- The e-liquids are stocked in many local shops, supermarkets and pharmacies. We are unable to provide an exhaustive list of suppliers but an example of some suppliers in the Newcastle area include (correct as of August 2016):
  - WHSmiths (Central station, Northumberland St.)
  - Sainsburys (Central station, Northumberland St., Gosforth)
  - Boots (Haymarket)
  - One stop/ post office (Two ball Lonnen)
  - McColls (Fawdon, Pilgrim St.)
  - Asda (Gosforth)
  - BP Service Station (Ponteland Road)

How to fill the e-cigarette

Charging the battery

- First detach the eTank clearomiser (tank) from the eTank battery.
- Screw the eTank battery onto your USB charging cable, twisting the battery in a clockwise direction. Take care not to over-tighten.
- Connect the other end of the USB charging cable to the USB port of a computer or the UK plug provided.
- Charging = red light on USB (battery light flashes and turns white)
- Fully charged = green light on USB (battery light flashes 10 times and then turns off)
- It should take no longer than 4 hours to fully charge.

What do ther battery lights mean?

- White- Fully charged
- Amber- Running low
- Flashing Red- Needs a recharge

Replacing the clearomiser (tank)

- This should be replaced every 2-4 weeks depending on use.
- You have been provided with one spare clearomiser.
- You will need to purchase replacement clearomisers from the manufacturer's website or local shops.
- If you accidently pour e-liquid into the central tube (this is difficult to do) the e-cigarette may stop working and you will need to replace the clearomiser.

Top tips for new users!

1. Don't overfill the clearomiser (tank), this can flood the e-cigarette.
2. Keep your battery charged. You should need to charge your e-cigarette about once a day.
3. If you get e-liquid on your skin, wash with plenty of soap and water.
4. As you hold down the button to vape you might hear a little crackling; this is a normal sound of the e-cigarette vaporising the e-liquid.
5. Be flexible with flavours. Find what works for you.
6. Be organised. Make sure you have a sufficient supply of e-liquid and replacement clearomisers.
7. It is normal to experience a 'throat hit' similar to smoking.
8. Keep your battery terminal clean. Use a cotton bud to clean away any debris.

Need more help?

- The manufacturers customer service team can be contacted on 0800 1337 350.

Appendix K E-cigarette intervention discussion guide

1	'You have been allocated to receive an e-cigarette as part of this study'
2	'We want you to 'switch' to e-cigarettes'
3	'You are still free to use any of the other ways to stop you want to use on top of this'
4	*Provide E-cigarette starter kit including:* - *Vype eTank starter kit* - *Spare battery* - *Spare Clearomiser* - *UK plug*
5	*Provide 'E-cigarette user guide'*
6	'We have produced this users guide.'
7	Page 2- 'This shows what you have included in the kit' 2 batteries, 2 tanks, plug, usb charger, 2 bottles of e-liquid (we still need to select these)'
8	'Can you please check the seal on the kit and open it'
9	'You are allowed two bottles of e-liquid. Which ones do you want?'
10	*Selection of e-liquids based on preference and nicotine concentration.*
11	'First I'm going to show you how to charge the batteries' [Demonstration]
12	'There are various colours of lights on the battery and charger' 'This is what they mean' [use page 5 of users guide]
13	'Next I'm going to show you how to put e-liquid into the device' [use page 4 of the users guide]
14	*Get participant to load liquid into device.*
15	'Finally I wanted to highlight a few items from the users guide'
16	'There is a manufacturers users guide at the back of the box that I recommend you read'
17	'It's really important you only use this charger'
18	'The date on the products is the date of manufacturer, not the expiry date. This can be a little confusing'
19	'We have provided you with two bottles of e-liquid which would last most people between 2-4 weeks. You will need buy your own e-liquid after these run out. We would like you to use only Vype e-liquids in this e-cigarette. The easiest place to buy these are the website which is detailed here [page 3]. There are also many shops which sell them and here are a few examples [page 3]. You are free to try any of their 9 flavours and any strength.

20	‘you have one spare tank. These should last around 2-4 weeks. You will need to buy some more spare ones, which can be purchased here [page 3].’
21	‘we have also listed some top tips here [page 6- read list]’
22	‘Do you have any questions?’

Appendix L Informed Consent Form

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Newcastle University

Insert patient sticker here

Patient Identification Number for this trial: 1 | | | |

CONSENT FORM

Title of Project: **A mixed methods feasibility study of electronic cigarette use by patients with periodontitis.**

Principal Investigator: Professor Philip Preshaw

Chief Investigator: Dr Richard Holliday

Please initial all boxes

1. I confirm that I have read and understand the information sheet dated __/__/____ (version ____) for the above study. I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time without giving any reason, without my medical care or legal rights being affected. ☐

3. I understand that relevant sections of my medical notes and data collected during the study may be looked at by individuals from the research team, from regulatory authorities or from the NHS Trust, where it is relevant to my taking part in this research. I give permission for these individuals to have access to my records. ☐

4. I understand that the information collected about me will be used to support other research in the future, and may be shared anonymously with other researchers. ☐

5. I agree to the use of audio recording, with possible use of anonymous verbatim quotation in publications. ☐

6. I agree to the storage and use of anonymous samples (saliva and gingival crevicular fluid) prospectively in a number of future projects. ☐

7. I agree to clinical photographic images being taken of me and anonymous copies being used in publications, including all forms of electronic publications. ☐

8. I agree to the transfer of anonymous samples to countries outside of the European Economic Area (EEA). ☐

9. I agree to my General Medical and Dental Practitioners being informed of my participation in the study. ☐

10. I agree to my mobile phone number being used to send me the weekly questions. Automatic software will be used to do this. ☐

11. I agree to take part in the above study. ☐

12. I would like a newsletter updating me of the progress of the study to be sent to me during and at the end of the study. **Y / N**

If so please provide an email or postal address:

_____

_____

_____	_____	_____
Name of Participant	Date	Signature
_____	_____	_____
Name of person taking consent.	Date	Signature

Original to be kept by the researcher, copy to be given to the participant.

Appendix M Participant commitment form

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Newcastle University

Insert patient sticker here

Patient Identification Number for this trial: | | | |

Commitment form

Title of Project: **A mixed methods feasibility study of electronic cigarette use by patients with periodontitis.**

Principle Investigator: Professor Philip Preshaw

Chief Investigator: Dr Richard Holliday

IRAS Number: 199724

Please read this form carefully and enter the information required in the spaces provided.

I _____ *(insert name)* understand that the purpose of this study is to advance our knowledge on which treatments are most effective at helping people to quit smoking.

I therefore commit to using the treatment that has been allocated to me.

I agree not to use the following smoking cessation treatments that have not been allocated to me, for at least the first four weeks from my target quit date:

_____
(list treatments not to be used, as discussed with researcher)

I am aware that using a treatment not allocated to me may make it difficult for the research team to interpret the findings of the study accurately.

_____ _____ _____
Participant Name (please print) Signature Date

Appendix N FTND questionnaire

The Newcastle upon Tyne Hospitals NHS
NHS Foundation Trust

Newcastle University

Farerstrom Test for Nicotine Dependance

Patient Identification Number for this trial: 1 ☐☐☐

Date completed: _____

	Please tick one box for each question		
How soon after waking do you smoke your first cigarette?	Within 5 minutes 5-30 minutes 31-60 minutes	☐ ☐ ☐	3 2 1
Do you find it difficult to refrain from smoking in places where it is forbidden? E.g. Church, Library, Etc.	Yes No	☐ ☐	1 0
Which cigarette would you hate to give up?	The first in the morning Any other	☐ ☐	1 0
How many cigarettes a day do you smoke?	10 or less 11-20 21-30 31 or more	☐ ☐ ☐ ☐	0 1 2 3
Do you smoke more frequently in the morning?	Yes No	☐ ☐	1 0
Do you smoke even if you are sick in bed most of the day?	Yes No	☐ ☐	1 0
	Total Score:		

Form completed by:

_____ _____ _____

Name Date Signature

Title of Project: **A mixed methods feasibility study of electronic cigarettes use by patients with periodontitis.**

Principle Investigator: Professor Philip Preshaw. Chief Investigator: Dr Richard Holliday

IRAS Number: 199724

Appendix O MPSS questionnaire

Mood and Physical Symptoms Scale (MPSS) Questionnaire

Patient Identification Number for this trial: | | | |

Date completed: _____

Please show for each of the items below how you have been feeling over the past 24 hours.
(Circle one number for each item).

	Not at all	Slightly	Somewhat	Very	Extremely
1. Depressed	1	2	3	4	5
2. Anxious	1	2	3	4	5
3. Irritable	1	2	3	4	5
4. Restless	1	2	3	4	5
5. Hungry	1	2	3	4	5
6. Poor concentration	1	2	3	4	5
7. Poor sleep at night	1	2	3	4	5

8. How much of the time have you felt the urge to smoke in the past 24 hours? ***(Circle one number)***

Not at all	A little of the time	Some of the time	A lot of the time	Almost all the time	All the time
0	1	2	3	4	5

9. How strong have the urges been? ***(Circle one number)***

No urges	Slight	Moderate	Strong	Very strong	Extremely strong
0	1	2	3	4	5

Have you experienced any of the following over the past 24 hours? (*Circle one number for each item*).

	No	Slight	Moderate	Severe	Very severe
10. Sores in the mouth	1	2	3	4	5
11. Constipation	1	2	3	4	5
12. Cough/sore throat	1	2	3	4	5

Form completed by (research staff to sign):

_____ _____ _____

Name Date Signature

Appendix P OHQoL-UK

The United Kingdom Oral Health-related Quality of Life Measure©

(Self-completion version)

Patient Identification Number for this trial: ☐☐☐

Date completed: _____

The next set of questions is about how your oral health (that is you teeth, gums, mouth and/or false teeth) may have affected your quality of life.* Remember there is no right or wrong answer.

	Rate the effect				
What effect (at present), if any, does your oral health have on your…….	*Very Good*	*Good*	*None*	*Bad*	*Very Bad*
…… eating or enjoyment of food?	○	○	○	○	○
…… appearance?	○	○	○	○	○
…….speech?	○	○	○	○	○
…….general health?	○	○	○	○	○
…….ability to relax or sleep?	○	○	○	○	○
…….social life?	○	○	○	○	○
…….romantic relationships?	○	○	○	○	○
…… smiling or laughing?	○	○	○	○	○
…… confidence?	○	○	○	○	○
…… carefree manner (lack of worry)?	○	○	○	○	○
…… mood?	○	○	○	○	○
…… work or ability to do your usual jobs?	○	○	○	○	○
…… finances?	○	○	○	○	○
…… personality?	○	○	○	○	○
…… comfort?	○	○	○	○	○
…… breath odour?	○	○	○	○	○

Form completed by (research staff to sign): _____ _____ _____

Name Date Signature

Study title: Feasibility study of e-cigarettes in periodontitis. IRAS number: 199724.
OHQoL questionnaire date of issue: 24/08/2016
OHQoL questionnaire version number: 1.2
Page 1 of 1

Appendix Q TOC charter

Feasibility study of e-cigarettes in Periodontitis

A mixed methods feasibility study of electronic cigarette use by patients with periodontitis.

ISRCTN 17731903

Trial Oversight Committee Charter

Version 1.0, Date 13.10.2016

(developed using Newcastle Clinical Trials Unit template TSC Charter version 1.02, 13-Mar-2006;
From DAMOCLES DMC Charter template V1, Feb 2005)

Prepared by

Name:	Richard Holliday	Role:	Chief Investigator
Signature:		Date:	13.10.2016

CONTENT	DETAILS OF TOC
1. Introduction	
Name of trial	A mixed methods feasibility study of electronic cigarette use by patients with periodontitis.
Objectives of trial, including interventions being investigated	**Trial aim/hypothesis** This trial aims to assess the feasibility of providing an e-cigarette to patients with periodontitis who smoke, as a smoking cessation/ harm reduction tool. This feasibility study will provide essential information on the practicality of running a full scale trial and provide data on study design, the distributional properties of the proposed outcome measures, e-cigarette acceptability, recruitment and retention. This trial and the future definitive trial will help inform the active debate around e-cigarettes. The objectives of the feasibility study are: • To estimate the eligibility rates among our patient population. • To assess patients' willingness to enter the trial • To estimate the recruitment rate; can 80 eligible patients be recruited in a 12 month period? • To ascertain if any participation biases exist. • To ascertain the retention rate of the participants for 6-month follow-up data? • To ascertain the randomised group contamination rates (i.e. the extent of cross-over between the two arms of the trial). • To test a weekly smoking status data collection method. • To compare descriptively novel and traditional periodontal outcome measures. (Novel: PISA, PESA. Traditional: PPDs. • To estimate the standard deviation of the periodontal outcome measures to input to the sample size calculation for future definitive trials. • To complete exploratory analyses of the distribution of the microbiome. • To complete exploratory analyses of the distributional properties of the inflammatory biomarkers. • To ascertain participant compliance when provided with an EC. • To describe tobacco smoking and EC usage. • To ascertain participant behaviour regarding the use of the EC: straight nicotine replacement or nicotine cessation device? • To complete a *Qualitative Process Evaluation* to establish the views of participants on the provision of e-cigarettes and to finalise the exact characteristics of an EC intervention for the future definitive study for this patient group. The outcome measure being assessed (described and variability assessed) by this study are: • Pocket Probing Depths (PPDs) • Gingival Index [Lobene Modified Gingival Index] • Plaque index [Silness and Low plaque index] • Clinical Attachment Loss • Bleeding on Probing

CONTENT	DETAILS OF TOC
	• Clinical Oral Dryness Score • Periodontal Epithelial Surface Area (PESA) • Periodontal Inflammed Surface Area (PISA) • Cumulative burnt tobacco use • Cumulative e-cigarette use • Expired Carbon monoxide • Salivary Cotinine • Salivary Anabasine • Fagerstrom Test for Nicotine Dependance (FTND) • Mood and Physical Symptoms Scale (MPSS) • Microbiological outcome measure • Inflammatory biomarkers • Oral health quality of life assessment • Theoretical domains framework participant interviews • Participant focus group • Staff feedback A participant flow diagram is shown in Figure 1.
Outline of scope of Charter	The purpose of this document is to describe the membership, terms of reference, roles, responsibilities, authority, decision-making and relationships of the Trial Oversight Committee (TOC) for this trial, including the timing of meetings, methods of providing information to and from the TOC, frequency and format of meetings and relationships with other trial committees.
Facilitation	Richard Holliday will act as the facilitator for this trial. The Facilitator will be responsible for the organisation of meetings and should be copied into all communications with and between the TOC.
2. Roles and responsibilities	
A broad statement of the aims of the TOC	To act as the oversight body for this trial on behalf of the Sponsor/Funder. The TOC will act as the Trial Steering Committee (TSC) and Data Monitoring Committee (DMC) for this study (as agreed by the study sponsor).
Terms of reference	The role of the TOC is to provide oversight for the trial. It should also provide advice through its independent Chairman to the Trial Management Group (TMG), Funder, Sponsor and NCTU on all aspects of the trial.
Specific roles of TOC	• provide expert oversight of the trial • maintain confidentiality of all trial information that is not already in the public domain • make decisions as to the future continuation (or otherwise) of the trial/s • monitor recruitment rates and encourage the TMG to develop strategies to deal with any recruitment problems • review regular reports of the trial from the Trial Management

CONTENT	DETAILS OF TOC
	Group (TMG). • assess the impact and relevance of any external evidence provided by TMG • monitor completion of CRFs and comment on strategies from TMG to encourage satisfactory completion in the future • monitor follow-up rates and review strategies from TMG to deal with problems • approve any amendments to the protocol, where appropriate • approve any proposals by the TMG concerning any change to the design of the trial, including additional sub-studies • oversee the timely reporting of trial results • comment on the statistical analysis plan • review / comment on the publication policy • review / comment on the main trial manuscript • review external or early internal requests for release of data or subsets of data or samples including clinical data and stored biological samples
3. Before or early in the trial	
Whether the TOC will have input into the protocol	All potential independent TOC members should have opportunity to comment on the protocol as early as possible. Before recruitment begins the trial will have undergone review by the Sponsor/Funder (e.g. peer review for public sector trials), scrutiny by other trial committees and a research ethics committee. Therefore, if a potential independent TOC member has major reservations about the trial (e.g. the protocol, the logistics, ethical concerns) they should report these to NCTU and may decide not to accept the invitation to join. TOC members should be constructively critical of the ongoing trial, but also supportive of aims and methods of the trial.
Trial specific issues	
Any issues specific to the disease under study	Periodontal disease is a common condition that is regularly managed by dentists. Patients who smoke are likely to present with more severe disease. No specific trial issues exist.
Any specific regulatory issues	This study has gained regulatory approval from NHS ethics and governance approval from the HRA.
Any other issues specific to the treatment under study	E-cigarettes are a topical issue and can attract a lot of press attention. It is likely that during the course of the study there will be news reports about e-cigarettes which may be negative. The study participants will be warned about this in the participant information sheet. The TMG will constantly review the literature and report back to the TOC. The UK Electronic Cigarette Research Forum (UKECRF- supported by Cancer Research UK, Stirling University and UKCTAS [UK Centre for Tobacco and Alcohol Studies]) publish a monthly research briefing of relevant research which will allow rapid identification of potential new information. Richard Holliday is a member of the UKECRF and UKCTAS.
Whether members of the TOC will have a contract	TOC members will not be asked to formally sign a contract but should formally register their agreement to join the group by

CONTENT	DETAILS OF TOC
	confirming (1) that they agree to be a member of the TOC and (2) that they agree with the contents of this Charter. Any potential competing interests should be declared at the same time and will be reviewed and confirmed by each member at every subsequent meeting. Members should complete and return the form in Annexes 1 or 2. Attendees and observers with no voting rights should complete and return the form in Annexes 3 or 4. Any attendees or observers (those who are not members) will sign a confidentiality agreement on the first occasion they attend a meeting.
4. Composition	
Membership and size of the TOC	The majority of members of the TOC, including the Chair, will be independent of the trial (see section 5). Non-independent members will also be part of the TOC. The independent members of the TOC for this trial are: (1) Independent Clinician – Professor Val Clerehugh, Professor of periodontology, University of Leeds. (2) Independent Statistician – Dawn Teare, Reader in Epidemiology and Biostatistics, The University of Sheffield. (3) Independent Patient Advisory Group Representative/ Lay Member – TBC (4) Independent Patient Advisory Group Representative/ Lay Member – TBC Non-independent members (with no voting rights): (1) Chief Investigator – Dr Richard Holliday, NIHR Doctoral Research Fellow/ StR in Restorative Dentistry, Newcastle University. (2) Principal Investigator- Professor Philip Preshaw, Professor of Periodontology, Newcastle University. (3) Trial Statistician- Vicky Ryan, Senior Statistician, Newcastle University. Attendees (with no voting rights): 1) Professor Elaine McColl – Professor of Health Service Research, Newcastle University. 2) Professor Falko Sniehotta, Professor of Health Behaviour and Health Psychology, Newcastle University. 3) Professor Linda Bauld, Professor of Health Policy, Stirling University. 4) Senior Trials Manager, Newcastle Clinical Trials Unit. And any other members of the TMG as invited. Invited observers (with no voting rights): 1) Sponsor Representative 2) Funder Representative
The Chair, how they are chosen and the Chair's role.	The Chair should have previous experience of serving on trial committees and experience of Chairing meetings, and should be able to facilitate and summarise discussions; knowledge of the disease area would be beneficial.

CONTENT	DETAILS OF TOC
The responsibilities of the Facilitator	The Facilitator will be Richard Holliday. The Facilitator will be responsible for arranging meetings of the TOC, coordinating reports, producing and circulating minutes and action points. The Facilitator will be the central point for all TOC communications between the TOC and other bodies, will be copied into all correspondence between TOC members and will be kept aware of trial issues as they arise.
The responsibilities of the CI and other members of the TMG	The CI is an important member of the TOC and no major decisions should be made without their involvement. The TMG/CI will produce a short report on the trial before each meeting of the TOC. A template report will be agreed at the first meeting of the TOC.
The responsibilities of the observers	Additional observers may be in attendance through (parts of) the TOC meetings in order to provide input.
5. Relationships	
Relationships with Chief Investigators, other trial committees (e.g. TMG), Sponsor/Funder and regulatory bodies	The responsibilities of each trial committee are detailed in the protocol and in the respective Charters.
Advisory and executive bodies	The TOC is the oversight body and is delegated the roles in Section 2 by the Sponsor. All substantial issues regarding the trial must go to the TOC for consideration.
Payments to TOC members	Members will be reimbursed for reasonable travel costs where required. No other payments or rewards are given.
The need for TOC members to disclose information about any real or potential competing interests	Any competing interests, both real or potential, should be disclosed. These are not restricted to financial matters – involvement in other trials or intellectual investment could be relevant. Although members may well be able to act objectively despite such connections, complete disclosure enhances credibility. (See Annex 1) TOC members should not use any trial data to inform trading in pharmaceutical shares, and careful consideration should be given to trading in stock of companies with competing products. Changes in declarations of real or potential competing interests should be minuted at the start of each meeting.
6. Organisation of meetings	
Expected frequency of TOC meetings	The TOC will meet six months after the start of randomisation and then at least once every nine months. At the request of the TOC, interim meetings, in person or by teleconference, will be organised (a teleconference will be arrange at three months at the request of the TOC). Major trial issues may need to be dealt with between meetings. Such issues will be dealt with via telephone or email correspondence. TOC members should be prepared for such

CONTENT	DETAILS OF TOC
	instances.
Attendance of TOC members at meetings	Effort will be made to ensure that all members can attend. The Facilitator will work for a date that enables this. The CI must try to attend all meetings, especially if major actions are expected. Members who cannot attend in person should be encouraged to participate by teleconference. If, at short notice, any TOC members cannot attend then the TOC may still meet if at least two independent members, including the Chair (unless otherwise agreed). If the TOC is considering a major action after such a meeting the TOC Chair should communicate with the absent members, including the CI, as soon after the meeting as possible to check they agree. If they do not, a further teleconference should be arranged with the full TOC.
How TOC meetings will be organised, especially regarding open and closed sessions, including who will be present in each session	Presence will usually be limited to the TOC members, observers from the Sponsor/Funder, Newcastle Clinical Trial Unit and the Facilitator. Other attendees may be invited for all or part of the meeting by the TOC. The observers are not members of the TOC but may be invited to provide expert input or to represent the funding bodies involved.
Can TOC members who cannot attend the meeting input	When the report is circulated before the meeting, TOC members who will not be able to attend the meeting may pass comments to the TOC Chair or CI for consideration during the discussions.
What happens to independent members who do not attend meetings	If an independent member does not attend a meeting or provide comments when requested between meetings, it should be ensured that the independent member is available for the next meeting. If an independent member does not attend the next meeting or provide comments when next requested, they should be asked if they wish to remain part of the TOC. If an independent member does not attend a third meeting, consideration should be given to replacing this member.
7. Trial documentation and procedures to ensure confidentiality and proper communication	
Intended content of material to be considered during meetings	A short report will be prepared by the CI following a standard template. This will report on accrual and any matters affecting the trial. Additionally, the material may include a report the TMG or draft publications.
Whether reports to the TOC be available before the meeting or only at/during the meeting	It is usually helpful for the TOC to receive the report at least 1 week before any meetings.
Responsibility for identifying and circulating external evidence (e.g. from other trials/ systematic reviews)	Identification and circulation of external evidence (e.g. from other trials/ systematic reviews) is not the responsibility of the TOC members; it is a responsibility of the TMG. However, the TOC should continue to be made aware of other data that may impact on a trial.
To whom the TOC will communicate the decisions that are made	The TOC will report their decisions (via the Facilitator) to the TMG (See Section 9 for details)
What will happen to the papers	TOC members would be expected to delete, destroy or store securely

CONTENT	DETAILS OF TOC
after the meeting	copies of the reports to and from the TOC, agenda and minutes, as well as copies of communications between meetings. All documentation should be considered confidential. The Facilitator will keep a central record of all minutes, reports and correspondence by the TOC.
8. Decision making	
What decisions will be open to the TOC	Based on the data presented on recruitment, follow-up and data quality possible decisions include:- • No action needed, trial continues as planned • Modifying target recruitment, or pre-analysis follow-up, based on any change to the assumptions underlying the original trial design. Sanctioning and/or proposing protocol changes Based on other factors, possible decisions include the decisions above and:- • Approving proposed protocol amendments or new trial sub-studies • Approving requests for early release of (subsets of) data • Approving presentation of results during the trial or soon after closure • Approval of new strategies to improve recruitment or follow-up
How decisions or recommendations will be reached within the TOC	Every effort should be made to achieve consensus. The role of the Chair is to summarise discussions and encourage consensus; therefore, it is usually best for the Chair to give their own opinion last. It is important that the implications (e.g. ethical, statistical, practical, financial) for the trial be considered before any decision is made.
When the TOC is quorate for decision-making	At least two independent members of the TOC should be present including the Chair, and if major action is to be considered, the CI.
Any specific issues relating to the trial design that might influence the proceedings	(See Section 3)
9. Reporting	
To whom will the TOC report their recommendations/decisions, and in what form	The TOC will report their decisions (via the Facilitator) to the TMG (in time for consideration at the next TMG Meeting) who will be responsible for implementing any actions resulting. The TOC may also provide feedback to the Sponsor/Funder. Copies of communications will pass through the Facilitator.
Whether minutes of the meeting be made and, if so, by whom and where they will be kept	Notes of key points and actions will be made by the Trial Management Team. This will include details of whether potential competing interests have changed for any attendees since the previous meeting. The draft minutes will be initially circulated for comment to those TOC members who were present at the meeting. The TOC Chair will sign off the final version of minutes or notes.

CONTENT	DETAILS OF TOC
10. After the trial	
Publication of results	The TOC will oversee the timely analysis, writing up and publication of the main trial results. The independent members of the TOC will have the opportunity to read and comment on the proposed main publications of trial data prior to submission. This review may be concurrent to that of the trial investigators.
The information about the TOC that will be included in published trial reports	TOC members will be named and their affiliations listed in the main report, unless they explicitly request otherwise.
Any constraints on TOC members divulging information about their deliberations after the trial has been published	All deliberations and discussions within the TOC will remain confidential unless released into the public domain through peer reviewed presentation/publication.

Abbreviations and glossary

CI	Chief Investigator
CRF	Case Report Form
ISRCTN	International standard randomised controlled trial number
TMG	Trial Management Group

Annex 1: Agreement and competing interests form for independent members

Feasibility study of e-cigarettes in periodontitis

Agreement to join the Trial Oversight Committee as an independent member and disclosure of potential competing interests

Please complete the following document and return to the TOC Facilitator.
(please initial box to agree)

	I have read and understood the TOC Charter version xx.x, dated __/___/____
	I agree to join the Trial Steering Committee for this trial as an independent member
	I agree to treat all sensitive trial data and discussions confidentially

The avoidance of any perception that independent members of a TOC may be biased in some fashion is important for the credibility of the decisions made by the TOC and for the integrity of the trial.
Potential competing interests should be disclosed via the CTU. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) independent TOC member should remove the conflict or stop participating in the TOC. Table 1 lists potential competing interests.

	No, I have no potential competing interests to declare
	Yes, I have potential competing interests to declare (please detail below)

Please provide details of any potential competing interests:

_____

_____

_____

Name: _____

Signed: _____ Date: _____

Table 1: Potential competing interests for independent members

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor/Funder
- Ongoing advisory role to a company providing drugs to the trial
- Frequent speaking engagements on behalf of the intervention
- Career tied up in a product or technique assessed by trial
- Hands-on participation in the trial
- Involvement in the running of the trial
- Emotional involvement in the trial
- Intellectual conflict e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) or career tied up in competing products
- Involvement in the writing up of the main trial results in the form of authorship

Annex 2: Agreement and competing interests form for non-independent members

Feasibility study of e-cigarettes in periodontitis

Agreement to join the Trial Oversight Committee as a non-independent member and disclosure of potential competing interests

Please complete the following document and return to the Facilitator.
(please initial box to agree)

	I have read and understood the TOC Charter version xx.x, dated __/___/____
	I agree to join the Trial Oversight Committee for this trial as an non-independent member
	I agree to treat all sensitive trial data and discussions confidentially

The avoidance of any perception that members of a TOC may be biased in some undisclosed fashion is important for the credibility of the decisions made by the TOC and for the integrity of the trial.

Possible competing interests should be disclosed via the NCTU. In many cases simple disclosure up front should be sufficient. Otherwise, the (potential) independent TOC member should remove the conflict or stop participating in the TOC. **Table 1** lists potential competing interests.

	No, I have no competing interests to declare other than involvement in the trial
	Yes, I have competing interests to declare (please detail below)

Please provide details of any competing interests:

_____

_____

_____

Name: _____

Signed: _____ Date: _____

Table 1: Potential competing interests for non-independent members

- Stock ownership in any commercial companies involved
- Stock transaction in any commercial company involved (if previously holding stock)
- Consulting arrangements with the Sponsor/Funder
- Ongoing advisory role to a company providing drugs to the trial
- Frequent speaking engagements on behalf of the intervention
- Intellectual conflict e.g. strong prior belief in the trial's experimental arm
- Involvement in regulatory issues relevant to the trial procedures
- Investment (financial or intellectual) in competing products

Annex 3: Agreement and confidentiality agreement for attendees

Feasibility study of e-cigarettes in periodontitis Trial Oversight Committee

Agreement to attend the Trial Oversight Committee and treat all information confidentially

Please complete the following document and return to the Facilitator.

(please initial box to agree)

	I have received a copy of the TOC Charter version xx.x dated __/___/____
	I am a member of the Trial Management Group
	I agree to attend the Trial Oversight Committee meeting
	I agree to treat as confidential any sensitive information gained during this meeting unless explicitly permitted

Name: _____

Signed: _____ Date: _____

Annex 4: Agreement and confidentiality agreement for observers

Feasibility study of e-cigarettes in periodontitis Trial Oversight Committee: Agreement to attend the Trial Oversight Committee and treat all information confidentially

Please complete the following document and return to the Facilitator.

(please initial box to agree)

	I have received a copy of the TOC Charter version xx.x dated __/___/____
	I agree to attend the Trial Oversight Committee meeting
	I agree to treat as confidential any sensitive information gained during this meeting unless explicitly permitted

Name: _____

Signed: _____ Date: _____

Appendix R Study Protocol

Study Protocol

A mixed methods feasibility study of electronic cigarette use by patients with periodontitis.

Short title/Acronym:	Feasibility study of e-cigarettes in Periodontitis.
Clinical Trials Registration Number:	ISRCTN 17731903
Version Number:	1.3
Date:	06/04/2017
IRAS Number:	199724
Funder:	NIHR (DRF-2015-08-077)
Investigators:	Dr Richard Holliday (Chief Investigator) Professor Philp Preshaw (Principal Investigator) Professor Elaine McColl (Co-investigator) Dr Falko Sniehotta (Co-investigator) Vicky Ryan (Co-investigator) Professor Linda Bauld (Co-investigator) Dr Nicholas Jakubovics (Co-investigator) Dr Suzanne McDonald (Co-investigator)
Sponsor:	Newcastle Upon Tyne NHS Foundation Trust
Representative of the Sponsor:	Susan Ridge Research Management and Governance Manager Newcastle upon Tyne Hospitals NHS Foundation Trust **Newcastle Joint Research Office,** Regent Point, Regent Farm Road, Newcastle upon Tyne, NE3 3HD.
REC reference:	
Site:	Dental Clinical Research Facility, Newcastle Dental Hospital, Newcastle Upon Tyne, Richardson Road. NE2 4AZ.

Trial Statistician:	Vicky Ryan
Clinical Trials Unit:	Newcastle Clinical Trials Unit (Registration number 22)

Contents

1. Introduction

1.1 Background

Periodontal diseases are highly prevalent and have a significant impact on the quality of life of large proportions of the population. For example 10% of the UK adult population suffer from severe forms of periodontal diseases. The pathogenesis is multifactorial and several key risk factors have been identified. Among these, tobacco smoking is the most important known risk factor. Smokers have consistently demonstrated more severe disease and increased tooth loss compared to non-smokers.

The development of electronic cigarettes (EC), devices that deliver a vapour containing nicotine, flavourings and diluents, has added a new option for smokers. No tobacco, smoke or combustion is involved in their operation.

ECs are the most popular quitting aid in smokers trying to stop smoking, with other types of quitting aids, such as nicotine patches and gum, seeing a significant decrease in usage (STS, 2015). ECs may be more attractive to smokers than traditional nicotine replacement therapies (NRT) as they not only replicate the pharmacological aspects of the addiction but also the psychosocial aspects such as the 'hand-to-mouth action' and the production of vapour/ smoke.

No clinical studies have been published to date that use electronic cigarettes in patients with periodontitis. This study is a mixed methods feasibility study, incorporating a pilot randomised controlled trial (RCT), with the aim of assessing the viability of delivering and studying the intervention prior to a definitive study. The focus of this study will be the deliverability, feasibility and acceptability of the e-cigarette intervention and of trial procedures (e.g. randomisation and data collection), rather than clinical efficacy or effectiveness of the intervention. It will not seek to produce any definitive results relating to the proposed interventions. If the current study indicates that the intervention and trial procedures are feasible and acceptable, a future RCT will be conducted to investigating the clinical effectiveness (in terms of smoking cessation and harm reduction rates) of electronic cigarettes in patients with periodontitis.

1.2 Clinical Data

Electronic cigarettes

There is a growing body of evidence suggesting EC may be an effective smoking cessation aid. A Cochrane collaboration systematic review concluded that e-cigarettes helped smokers to stop smoking and showed particular promise in reducing cigarette consumption in smokers unwilling to quit (McRobbie et al, 2014). Two randomised controlled trials (RCT) were included in this systematic review (Polosa et al, 2014; Bullen et al, 2013).

Polosa et al (2014) conducted a RCT of 300 smokers not intending to quit and compared the effect of a 12-week course of 7.2mg nicotine, 5.4mg nicotine and a nicotine free EC. Biochemically validated 6-month abstinence rates were 13%, 9% and 4% in the three groups, although there was no statistically significant difference between the groups.

Bullen et al (2013) conducted a RCT of 657 people, investigating the efficacy of e-cigarettes (16mg/ml) in smoking cessation compared to nicotine patches and found that abstinence rates were comparable with nicotine patches. This study was criticized for being underpowered and using a low nicotine delivery EC.

More recently a pilot study (Hajek et al, 2015) included EC (1.6mg/ml, 18mg/ml and 2.2mg/ml) within the treatment options offered to 100 smokers accessing support within a stop smoking service (SSS). 69% of the smokers took up the offer of an EC and 65% of these stopped smoking compared to 45% in those who declined the EC.

Ongoing studies include the TEC study (Hajek, 2015) at Queen Mary, University of London (18mg/ml starter e-liquid). This is a NIHR HTA funded trial to examine the efficacy of EC compared to nicotine replacement therapy (NRT), when used within the UK stop smoking service. This study plans to recruit 886 participants with a predicted trial end date of 31st March 2018.

Dentists providing smoking cessation interventions

Dentists, in a similar fashion to General Medical Practitioners (GMPs), are advised to provide brief advice interventions to their smoking patients. The national guidance from the National Centre for Smoking Cessation and Training (NCSCT) and National Institute of Clinical Excellence (NICE) advises dentists to deliver a Very Brief Advice (VBA) intervention (NCSCT, 2011; NICE, 2006).

A Cochrane review (Stead et al, 2013) looked at the effect of a brief advice intervention delivered by physicians. Data was pooled from 17 studies, and gave an Odds Ratio of 1.66 compared to no advice. Assuming an unassisted 6-month success rate of 3%, a brief advice intervention can increase the quit rates (6-month) to 5%.

Another Cochrane review (Carr and Ebbert, 2014) looked specifically at tobacco cessation in the dental setting and found high heterogeneity between studies (I^2 = 61%). When only looking at the six individually randomised trials, heterogeneity was reduced (I^2 = 27%), and gave an Odds Ratio of 1.46 compared to 'usual care, no contact, or less treatment intensive controls'. Again assuming an unassisted 6-month success rate of 3%, an intervention in the dental setting can increase the quit rates (6-month) to 4.4%.

Periodontitis and smoking

Periodontal diseases (gum disease) are one of the most common inflammatory conditions in humans. Periodontitis, an advanced form of periodontal disease, has a multifactorial aetiology but the principal process involves a dental plaque biofilm accumulating in the sub-gingival environment causing an immune and inflammatory response that leads to destruction of the supporting structures. Consequences of periodontal disease progression

include tooth mobility and eventually tooth loss. Severe periodontitis, threatening tooth retention, affects approximately 10% of UK adults; and moderate periodontitis affects 40-60% (Morris et al, 2009). A recent estimate calculated 4.4 million adults in the UK had severe disease (Griffiths & Preshaw, 2014).

There are multiple risk factors for periodontal diseases but cigarette smoking is the most important environmental risk factor and is thought to affect the periodontal tissues via multiple pathways, such as effects on the host immune and inflammatory response. Cigarette smokers experience impairment of the periodontal vasculature with lower oxygen tension and suppression of the normal inflammatory response to sub-gingival biofilm with reduced gingival redness, volume of gingival crevicular fluid and bleeding. When smokers quit, the local inflammatory response recovers quickly and they often experience a transient increase in gingival bleeding. Interestingly, nicotine alone has been shown to increase oxygen tension in the gingival tissues, unlike the effect of cigarette smoke. Neutrophils are critical cells in the maintenance of periodontal health and it is clear that cigarette smoke affects multiple functions of neutrophils that collectively contribute towards the tissue destruction seen in periodontitis. Cigarette smoking additionally reduces the healing potential of tissues, negatively impacting on fibroblast function and collagen synthesis.

Of particular relevance in the management of periodontitis is the knowledge that smokers who quit are 30% more likely to see clinically significant improvements than individuals who continue to smoke (Chambrone, 2013).

No clinical studies exist investigating the potential effect of EC vapour on the periodontal tissues. For the future definitive RCT our hypothesis would be that EC vapour is significantly less damaging than tobacco smoke. Additionally we would hypothesise that ECs are attractive to smoking patients with periodontitis (as a smoking cessation/reduction aid), leading to improved smoking cessation rates and periodontal treatment outcomes.

1.3 Rationale and Risk/ Benefits

Although there is an increasing amount of clinical research being conducted with ECs in many settings there is a total lack of any related to ECs within dental settings. Prior to conducting the definitive RCT summarised above, a feasibility study is required to obtain essential information on the practicality of running a full scale trial and to provide data (e.g. eligibility, consent and retention rates, variability of proposed primary outcome) to inform the design of future definitive studies.

It is fundamentally important that research is undertaken to understand how ECs fit within dental care. ECs are cheaper than a standard 12-week course of NRT and are more attractive to smokers. Additionally the use of traditional NRT and the use of specialist stop smoking services have seen significant declines in recent years (those setting a quit date through the SSS has almost halved over the last 3 years). Dentists find themselves in an important position, increasingly being the main (or only) professional contact a smoker will have.

EC use does not involve tobacco combustion, which is the primary source of the many thousands of dangerous chemicals to which smokers of conventional cigarettes are exposed. Studies on EC users have identified little or none of the known toxins associated with tobacco smoking [45], and while they may not be entirely safe, no serious health risks have been identified. Public Health England published an evidence review in August 2015 which concluded that EC were around 95% less harmful than smoking. There is little doubt that ECs are substantially safer than conventional cigarettes.

Patients who have periodontitis and are smokers are of particular importance due to the intimate relationship between the two and the potential for substantial health gains.

2 Trial Objectives and Design

2.1 Trial Objectives

The objectives relate to assessing the feasibility of the future definitive RCT. In particular:

- To estimate the eligibility rates among our patient population.
- To assess patients' willingness to enter the trial
- To estimate the recruitment rate; can 80 eligible patients be recruited in a 12 month period?
- To ascertain if any participation biases exist.
- To ascertain the retention rate of the participants for 6-month follow-up data?
- To ascertain the randomised group contamination rates (i.e. the extent of cross-over between the two arms of the trial).
- To test a weekly smoking status data collection method.
- To compare descriptively novel and traditional periodontal outcome measures. (Novel: PISA, PESA. Traditional: PPDs.
- To estimate the standard deviation of the periodontal outcome measures to input to the sample size calculation for future definitive trials.
- To complete exploratory analyses of the distribution of the microbiome.
- To complete exploratory analyses of the distributional properties of the inflammatory biomarkers.
- To ascertain participant compliance when provided with an EC.
- To describe tobacco smoking and EC usage.
- To ascertain participant behaviour regarding the use of the EC: straight nicotine replacement or nicotine cessation device?
- To complete a *Qualitative Process Evaluation* to establish the views of participants on the provision of e-cigarettes and to finalise the exact characteristics of an EC intervention for the future definitive study for this patient group.

2.2 Trial Design

This study is a mixed methods feasibility study, comprising a pilot randomised controlled trial (RCT) with embedded qualitative process evaluation. The participants will be smokers who have a diagnosis of Periodontitis (severe chronic) and are provided with a smoking cessation intervention alongside their standard periodontal therapy. This feasibility study will provide essential information on the practicality of running a full scale trial and provide

data on study design, the distributional properties of the proposed outcome measures, e-cigarette acceptability, recruitment and retention. The RCT is an individually randomised, 2-armed parallel group trial with a 1:1 allocation ratio. Outcome assessors will be blinded to participant allocation and smoking status. Participants will either receive usual care (UC; Very Brief Advice on Smoking and Oral Health [VBA-SOH]) or UC+EC (VBA-SOH and Electronic Cigarette Provision and Training [ECPT]).

3 Methods: Participants, interventions and outcomes

3.1 Study setting

This study will be completed within the Dental Clinical Research Facility (DCRF) of the Newcastle Dental Hospital (NDH), a secondary and tertiary care provider.

3.2 Eligibility criteria

Inclusion Criteria

- Aged over 18 years old
- Smoker of burnt tobacco (≥10 factory-made cigarettes/day or 7g [0.25 oz) loose tobacco/day or 14 hand-rolled cigarettes/day)
- Not currently using an EC, or not used one for more than two days in the last 30 days.
- Be willing and able to come to the Dental Clinical Research facility in the Newcastle Dental Hospital for the required study visits.
- Minimum of 16 natural teeth (excluding third molars)
- Diagnosed with severe chronic periodontal disease having interproximal pocket probing depths (PPDs) of ≥ 5mm at ≥ 8 sites.
- Have read, understood and signed an informed consent form

Exclusion Criteria

- Having used an e-cigarette for more than two days in the last 30 days;
- Infectious or systemic diseases that may be unduly affected by participation in this study.
- Haemodynamically unstable patients hospitalised with severe arrhythmias, myocardial infarction, cerebrovascular accident
- Suffering from Phaeochromocytoma.
- Suffering from uncontrolled hyperthyroidism.
- Liver or Kidney problems.
- Chronic Obstructive Pulmonary Disease.
- Patients taking the medication Adenosine
- Lack of capacity to be able to consent to the research project and/or inability to follow study instructions.

- Participation in a dental research study within the previous 20 days.
- Pregnant by medical history, or nursing.
- Received any non-surgical periodontal therapy other than a routine scale and polish in the last 6 months.
- Currently undergoing or requiring extensive dental, orthodontic or implant treatment, or treatment for peri-implantitis.

Eligibility Criteria requiring further discussions with individual participants.

- Asthma (Severity needs to be assessed. Patient made aware that NRT better than smoking but best to use NRT as a short term stop smoking treatment).
- Long term throat disease (Severity needs to be assessed. NRT use may exacerbate symptoms).
- Stomach Ulcer, duodenal ulcer, irritation or inflammation of the stomach or throat (NRT may exacerbate symptoms).
- Patient with diabetes mellitus will be advised to monitor their blood glucose more closely when initiating treatment. They will be advised to discuss this will their doctor or diabetic nurse.
- Patients taking medications metabolised by CYP 1A2 and that have a narrow therapeutic window can be effected by stopping smoking. Patients taking theophylline, clozapine and ropinirole will be asked to see their doctor to discuss changing the dose prior to starting the quit attempt.

3.3 Interventions

3.3.1 Intervention descriptions

Smoking cessation intervention

All participants in this study will receive usual care (UC) with regards to smoking cessation interventions. UC involves a brief intervention being delivered by the dentist alongside the dental care. Guidelines ([NCSCT, 2011], [BDA, 2015], [PHE, 2014a], [PHE, 2014b]) suggest this brief intervention follows the '3 A's': Ask, Advise, Act technique. A referral to Newcastle stop smoking services will be available. This intervention will be audio-recorded to allow tests for fidelity.

TiDier checklist- Very Brief Advice on Smoking and Oral Health

No.	Item	Definition
1	Brief Name	Very Brief Advice on Smoking and Oral Health (VBA-SOH)
2	Why	A Very Brief Advice intervention, within a medical setting, has been shown to have a significant increase in the rate of quitting (RR 1.66). Oral health care professionals are in an opportunistic position to deliver a smoking cessation intervention. They can provide advice

		to quit on medical grounds with very powerful patient specific prompts (e.g. radiographs). Specifically for patients with periodontitis, stopping smoking prior to the delivery of their periodontal intervention will lead to significant, visually obvious and relatively rapid improvements.
3	What (materials)	If the patient has a panoramic radiograph this will be used as a prompt to demonstrate any periodontal disease diagnosis, bone loss and likely impact of smoking on the mouth. If no radiographs are available then other prompts such as tooth staining and bad breath will be used as personal prompts.
4	What (procedure)	The VBA-SOH is a short behavioural based intervention based around three domains: 1. ASK- Ask and record the smoking status (current smokers, ex-smoker, non-smoker)? 2. ADVICE- - Advice on the likely impact of smoking on the mouth, specifically periodontitis. (Using patient specific prompts where appropriate e.g. panoramic radiograph) - Advice on the best way to quitting. (The best way of stopping smoking is with a combination of medication and specialist support). 3. ACT- Act on patient's response. Build confidence, give information and refer. They are up to four times more likely to quit successfully with support. Referral to the stop smoking services involves provision of information leaflets about the local stop smoking services including contact details. A suggested quit date of visit 2 (initial visit of periodontal therapy) will be suggested.
5	Who provided	A dentist or hygienist will provided the VBA-SOH. They have completed the National Centre for Smoking Cessation Training (NCSCT) e-learning module 'Very Brief Advice on Smoking'.
6	How	The VBA-SOH will be delivered at an individual level, by the dentist/hygienist, integrated as part of a dental visit.
7	Where	Dental Surgery, Newcastle Dental Hospital.
8	When and how much	The VBA-SOH will be specifically delivered during study visit 1 (the dental visit prior to the commencement of the periodontal therapy). During this visit the periodontal diagnosis will be discussed with the patient, oral hygiene instruction given and the VBA-SOH provided. The duration of the VBA will vary between 2-5 minutes depending on the response of the participant. The VBA-

		SOH will be reinforced at each subsequent dental visit and again this will be dependent on the individual participant.
9	Tailoring	The duration of the VBA-SOH will be dependent on the engagement of the individual participant. Participants will receive supportive advice, at follow up visits, tailored to their level of engagement. As a minimum a 30 second VBA will be delivered at each dental visit.
10	Modifications	NA
11	How well (Planned)	The VBA training was delivered by a national organisation. Dentists receiving training on discussing the effects of smoking on oral health as part of their undergraduate degrees. The VBA-SOH delivered during the first study visit will be audio-recorded and a sample checked for implementation fidelity against the VBA flow diagram.
12	How well (Actual)	NA

Control Group (UC)

Participants within the control group will receive the UC smoking cessation intervention (VBA-SOH) described above. Participants in the control group will be asked not to use an e-cigarette for the duration of the study, particularly the first 4 weeks, but this will not be completely prohibited (it would be impractical to do so, since they are freely available for purchase OTC). Participants will be asked to sign a commitment form at the same time as consent.

Intervention Group (UC+EC)

Participants within the intervention group will receive the same UC smoking cessation intervention (VBA-SOH) as the control group and will also be provided with a second generation EC and supply of e-liquid. The participants will be provided with a 2 week supply of liquid and information on where to buy more themselves. They will be instructed to use only the Vype brand of e-liquids for the duration of the study. At every contact point we have with the participants we will monitor which EC product is being used as well as the frequency and length of use.

TiDier Checklist- Electronic Cigarette provision and training

No.	Item	Definition
1	Brief Name	Electronic Cigarette Provision and Training (ECPT)
2	Why	EC have seen a significant rise in popularity in recent years and there is a growing body of evidence that they are an attractive and effective smoking cessation/ harm reduction tool. EC are easy for dentist's to provide and recommend.
3	What (materials)	The participants will be provided with a second generation (tank) EC. A starter kit will be provide which includes:

		- Vype eTank (CE marked) - 650mAh battery (x2) - USB charging cable - UK Plug - Spare Clearomizer - Manafacturers users guide Two 10ml bottles of e-liquid will be provided. There will be three flavour options (Blended Tobacco, Crisp Mint, Dark Cherry and Vpure [flavourless]). There will be a range of nicotine concentrations available (0mg/ml, 6mg/ml, 12mg/ml, 18mg/ml). The choice of initial liquid concentration will be decided on by discussion with the participant and review of their level of nicotine dependence. It is anticipated most participants will initially require 12mg/ml or 18mg/ml. An information sheet on setting up the EC will be provided. An information sheet on where to purchase further e-liquids will be provided.
4	What (procedure)	The dentist/ hygienist will provide the EC starter kit and e-liquid to each participant in the intervention arm of the study. They will practically demonstrate the EC set up with each participant. They will talk through the information sheets and answer any questions the participant has.
5	Who provided	A dentist or hygienist will provide the EC and training.
6	How	The EC training will be delivered as a conversation with the EC as a prompt.
7	Where	Dental Surgery, Dental Clinical Research Facility, Newcastle Dental Hospital.
8	When and how much	The ECPT will be delivered directly following the VBA-SOH intervention. The ECPT duration will be 10-15 minutes.
9	Tailoring	The ECPT will be the same for all participants. Some participants may require further support which could be requested at subsequent appointments as required.
10	Modifications	NA
11	How well (Planned)	The dentist/ hygienist providing the ECPT will follow the information sheet as a prompt. The ECPT will be audio-recorded and a sample checked for implementation fidelity.
12	How well (Actual)	NA

Periodontal intervention

All participants, regardless of arm, will receive identical routine non-surgical periodontal therapy. This will follow established and routine clinical management protocols that are already in use in the Dental Hospital. Thus, clinical care will not be altered in anyway by participation in the study. Patients initially undergo a period of patient education and motivation (oral hygiene instruction) which will follow a structured approach as described by Jönsson et al, 2009.

TiDier Checklist- Oral Hygiene Instruction

No.	Item	Definition
1	Brief Name	Oral Hygiene Instruction (OHI)
2	Why	Obtaining a satisfactory level of oral hygiene is an important factor in the success of periodontal interventions.
3	What (materials)	As appropriate: - Inter-dental cleaning aids: dental floss, inter-dental brushes - Single tuffed brush - Manual toothbrush (demo only) - Power toothbrush (demo only) - Demonstration model
4	What (procedure)	The dentist/ hygienist will present information on caries and gingivitis/periodontitis and oral hygiene instruction was given based on plaque disclosure. The individual's oral status was reviewed at the subsequent visits.
5	Who provided	A dentist or hygienist.
6	How	The OHI will be delivered as a face-to-face conversation at an individual level.
7	Where	Dental Surgery, Dental Clinical Research Facility, Newcastle Dental Hospital.
8	When and how much	The OHI will be delivered directly following the VBA-SOH (+/- ECPT) intervention. The OHI duration will be 5-10 minutes. At subsequent visits further OHI will be provided as appropriate, often integrated as part of the periodontal therapy.
9	Tailoring	The OHI will follow the same structure for all participants but will be tailored according to the participants existing level of oral hygiene, level of oral hygiene knowledge and level of engagement.
10	Modifications	NA
11	How well (Planned)	The dentist/ hygienist providing the OHI are experienced practitioners.
12	How well (Actual)	NA

The OHI is followed by debridement of the root surfaces of teeth under local anaesthetic. A Full Mouth Debridement (FMD) technique will be used where all the root

surface debridement is completed within a short time frame (ideally 24 hours) in line with local (Holliday, 2013) and international (Sanz and Teughels, 2008) guidance.

3.3.1.1 Participant withdrawal

Participants may withdraw from the study for any reason at any time. If they chose to withdraw they will be given the option of continuing with the study visits and assessments without any interventions. The investigator may also withdraw participants from the study in order to protect their safety (after discussion with Principle Investigator). Identifiable data or tissue already collected with consent would be retained and used in the study. No further data or tissue would be collected or any other research procedures carried out on or in relation to the participant. With the patients consent a letter detailing the treatment provided will be sent to the general dental practitioner and general medical practitioner.

3.3.2 Intervention adherence

This study is intended to be a pragmatic design and hence there will not be excessive participant follow up with regards to compliance. Participants being provided with the EC will be given an initial training session and a written instruction sheet.

To enhance the validity of study data, biochemical validation (expired carbon monoxide) of the participant's self-reported smoking status will be taken at 5 time points (baseline, suggested quit date, 4-weeks, 3-months, 6-months). A reading of 10 parts per million (ppm) or above signifies smoking burnt tobacco [50].

Additionally saliva samples will be taken at 4 time points (baseline, quit date, 4-weeks and 6-months). These saliva samples will have biochemical validation for cotinine and anabasine. Cotinine is a metabolite of nicotine and salivary cotinine is a biomarker of nicotine exposure and will give high readings in those using burnt tobacco, e-cigarettes or other nicotine replacement products. A reading below 15ng/ml signifies a non-user of burnt tobacco or nicotine products [50]. Salivary anabasine (<0.1ng/ml) can be used to confirm if a participant using NRT/ e-cigarettes has also obtained nicotine from tobacco [51][52]. This will allow us to verify self-reported smoking status of those who have abstained from all nicotine, those using only NRT/e-cigarettes and those still smoking burnt tobacco.

3.3.3 Concomitant care

Participants in the control group will be asked not to use an e-cigarette for the duration of the study, especially the first 4 weeks, but this will not be completely prohibited (it would be impractical to do so, since they are freely available for purchase OTC). Participants will be asked to sign a commitment form. The use of all services and cessation aids will be tracked in detail for all participants.

Participants in the intervention group (EC) will be instructed to use only the Vype brand of e-liquids for the duration of the study. At every participant contact we will monitor which EC product is being used as well as the frequency and length of use. The participants will be

free to use other Nicotine Replacement Products, either over the counter or through the specialist stop smoking services.

3.4 Outcomes

The following outcome measures will be described and variability assessed as part of determining suitable outcome measures for the future definitive study and to inform power calculations:

Measurement variable	Analysis metric	Method of aggregation	Time points	Clinical relevance
PPD (Pocket Probing Depths)	Change from baseline	Multiple analysis: - Mean PPD change - Proportion of sites improving by >2mm. - Proportion of deep sites (baseline PPD >6mm) improving by >2mm.	Baseline, 3-months, 6-months	Measure of periodontal health. Standard outcome measure for periodontal studies.
GI (Gingival Index [Lobene Modified Gingival Index])	Change from baseline	Means, Standard Deviation (SD) and 95% Confidence Intervals (CI) [within groups, not differences between groups]	Baseline, 3-months, 6-months	Measure of gingival health.
PI (Plaque Index [Silness and Low plaque index])	Change from baseline	Means, SD and 95% CI [within groups, not differences between groups]	Baseline, 3-months, 6-months	Measure of oral hygiene
CAL (Clinical Attachment Loss)	Change from baseline	Means, SD and 95% CI [within groups, not differences between groups]	Baseline, 3-months, 6-months	Measure of current and previous periodontal disease exposure.
BOP (Bleeding on Probing)	Change from baseline	Means, SD and 95% CI [within groups, not differences between groups]	Baseline, 3-months, 6-months	Measure of gingival health.

CODS- Clinical Oral Dryness Score	Change from baseline As described by Osailan et al, 2012.	Means, SD and 95% CI [within groups, not differences between groups]	Baseline, 3-months, 6-months	Measure of oral dryness.
PESA (Periodontal Epithelial Surface Area)	Change from baseline. Calculations as described by Nesse et al, 2008.	Means, SD and 95% CI [within groups, not differences between groups]	Baseline, 3-months, 6-months	Novel method of measuring periodontal health.
PISA (Periodontal Inflammed Surface Area)	Change from baseline. Calculations as described by Nesse et al, 2008.	Means, SD and 95% CI [within groups, not differences between groups]	Baseline, 3-months, 6-months	Novel method of measuring periodontal health.
Cumulative burnt tobacco use	- Total over the 6 months. - Units will be either cigarettes or oz of tobacco. - Calculations will be based on weekly self-reported data collected from the participant who will be asked to report their average cigarettes/day over the last 7 days.	Means, SD and 95% CI [within groups, not differences between groups]	Weekly data collection	Measure of burnt tobacco exposure over duration of the study.
Cumulative EC use	- Total over the 6 months. - Units will be at a daily level (did you use an EC today?) - EC days/ 6 months. - Calculations will be based on weekly self-reported data collection. A range from 0-182 will be possible.	Means, SD and 95% CI [within groups, not differences between groups]	Weekly data collection	Measure of EC exposure over duration of the study.

Expired air Carbon Monoxide (eCO)	- Change from baseline. - eCO readings at the 5 time points will be presented graphically.	Means, SD and 95% CI [within groups, not differences between groups]	Baseline, suggested quit date, 4-weeks, 3-months, 6-months	Measure of smoking status.
Salivary Cotinine (SC)	Change from baseline [Proportion of participants with readings below 15ng/ml.]	Means, SD and 95% CI [within groups, not differences between groups]	Baseline, suggested quit date, 4-weeks, 6-months	Measure of nicotine exposure (from tobacco, EC or NRT)
Salivary Anabasine (SA)	Change from baseline [Proportion of participants with readings below <0.1ng/ml.]	Means, SD and 95% CI [within groups, not differences between groups]	Baseline, suggested quit date, 4-weeks, 6-months	Measure of tobacco nicotine (Not EC & NRT)
Fagerstrom Test for Nicotine Dependence (FTND) Score out of 10.	Change from baseline	Means, SD and 95% CI [within groups, not differences between groups]	Baseline, suggested quit date, 4-weeks, 6-months	Measure of degree of dependence among smokers coming to a smoking cessation clinic and is extensively used in tobacco research (Heatherton et al, 1991).
Mood and Physical Symptoms Scale (MPSS)	Change from baseline. Calculations and analysis as described by West & Hajek, 2004 and NCSCT, 2012.	Means, SD and 95% CI [within groups, not differences between groups]	Baseline, suggested quit date, 4-weeks, 6-months	Measures the severity of urges to smoke and other tobacco withdrawal symptoms (West & Hajek, 2004).
Microbiological outcome measure (Micro)	Change from baseline	Exploratory presence and proportions of	Baseline, 3-months, 6-months	Indicates the pathogenic nature of the

		bacterial species present will be quantified.		Microflora.
Inflammatory biomarkers (IB): - interleukin (IL)- 1β - matrix metalloproteinase 8 (MMP-8)	Change from baseline	Means, SD and 95% CI [within groups, not differences between groups]	Baseline, 3-months, 6-months	Indicates the level of inflammation in the tissues.
Oral Health Quality of Life Assessment (OHQoL-UK)	Change from baseline	Means, SD and 95% CI for both summary score and the 16 individual items [within groups, not differences between groups]	Baseline, 6 months	Measure of oral health Related quality of life.
Theoretical Domains Framework (*TDF*) Participant Interviews	Participant responses at two time points (shortly after intervention delivery) and at a long term time point.	Qualitative analysis as described by Michie et al, 2005 and Cane et al, 2012.	4- week, 6-months	Investigates behaviour change.
Participant Focus Group	Participant's opinion gathered following completion of the study.	Qualitative analysis.	Post 6-month visit.	Optimise future intervention design.
Staff Feedback	Reflective log	Qualitative analysis.	Throughout	Optimise future intervention design.

3.5 Participant timeline

See figure 1 for a schematic participant flow diagram.

3.6 Sample size

No formal sample size calculation has been performed for this feasibility RCT as the primary outcome measures are concerned with the recruitment, randomisation and retention of patients to the trial and there is no intention to draw inferences regarding clinical efficacy or to compare clinical outcomes across arms.

Recommendations for good practice in feasibility trials (Lancaster et al, 2004) suggest 30 patients or greater are randomised to each arm of the trial to estimate standard deviations of key study parameters to input to sample size calculations for future definitive trial applications.

However, given the attrition rate for randomised patients in this study is not known (and is part of the feasibility assessment), 80 patients in total will be randomised, 40 to each arm of the trial, to allow for up to 25% attrition while achieving 30 patients per intervention arm with complete study follow-up.

3.7 Recruitment

80 participants will be recruited for this study. They will be recruited both directly through the new patient and treatment clinics of the Newcastle Dental Hospital but also by primary care practitioners (General Dental Practitioners, Therapists, Hygienists) identifying potentially eligible patients and referring directly to the Dental Clinical Research Facility.

4 Methods: Assignment of interventions Number of Subjects and Subject Selection

4.1 Sequence generation, Allocation concealment mechanism, Implementation

Following assessment of eligibility and completion of informed consent participants will be randomised to receive UC or UC+ECPT, in a 1:1 ratio using random permuted blocks. The randomisation allocation schedule will be generated by a statistician with no other involvement in the study to achieve concealment of allocation.

Randomisation will be performed by a member of site staff, appropriately trained and identified on the delegation log, using a secure password-protected web-based system administered by Newcastle Clinical Trials Unit (CTU). Randomisation will generate a unique 4-digit "Study ID number" for each participant. There are no stratification factors. The research hygienist will remain blinded to the participant allocation.

4.2 Blinding

Due to the nature of this study the participants and care providers will be unable to be blinded to assigned intervention. The outcome assessor, measuring the range of oral health indices, will be blind to participants smoking status and intervention allocation. These study measurements will be collected by a trained, blinded, calibrated research hygienist. At these visits participants will see the dentist, for any study interventions, and the research

hygienist, for clinical study measurements. Participants will be asked not to disclose their smoking status or methods of smoking cessation.

To achieve concealment of allocation, the randomisation allocation schedule will be generated by a statistician with no other involvement in the study and the randomisation will be administered independently by Newcastle CTU.

4.3 Data collection methods

PPD (Pocket Probing Depths)

A trained and calibrated hygienist, blinded to group allocation, will collect the PPDs using a manual UNC-15 periodontal probe to record the probing depths to the nearest. Probing depth is the distance from the probe tip (assumed to be at the base of the pocket) to the free gingival margin. Recorded at 6 sites per tooth.

GI (Gingival Index [Lobene Modified Gingival Index])

A full mouth gingival index will be recorded based on the Lobene Modified Gingival Index (Lobene et al, 1986) (MGI) rated on a scale of 0 to 4 (recorded at 6 sites per tooth):

0 = absence of inflammation

1 = mild inflammation; slight change in colour, little change in texture of any portion of but not the entire margin or papillary gingival unit

2 = mild inflammation; but involving entire margin or papillary unit

3 = moderate inflammation; glazing, redness, oedema and/or hypertrophy of margin or papillary unit

4= severe inflammation; marked redness, oedema and/or hypertrophy of marginal or papillary gingival unit, spontaneous bleeding, congestion, or ulceration]

PI (Plaque Index [Silness and Low plaque index])

The plaque index of Silness and Loe (Silness and Loe, 1986) will be employed to measure plaque (without disclosing) at 6 sites per tooth.

Scores will be assigned as follows:

0 = no plaque

1 = a thin film of plaque at the gingival margin which may be seen only after running the probe along the tooth surface

2 = moderate accumulation of plaque deposits which can be seen with the naked eye

3 = Extensive accumulation of plaque deposits

Gingival recession (used to calculate CAL outcome measure)

Gingival recession will be recorded to the nearest mm using a manual UNC-15 periodontal probe. Gingival recession is the distance from the free gingival margin to the cemento-enamel junction. Gingival recession will be indicated as a positive number and gingival overgrowth will be indicated as a negative number.

BOP (Bleeding on Probing)

Following probing, each site will be assessed for bleeding on probing, if bleeding occurs within 30s of probing, a score of 1 will be assigned for the site, otherwise, a score of 0 will be assigned. Recorded at 6 sites per tooth.

CODS- Clinical Oral Dryness Score

Oral dryness (xerostomia) will be measured using a 10 point scale as described by Osailan et al, 2012. A score of 1 is assigned for each of the following:

1) mirror sticks to buccal mucosa;

2) mirror sticks to tongue;

3) frothy saliva;

4) no saliva pooling in floor of mouth;

5) tongue shows loss of papillae;

6) altered/smooth gingival architecture;

7) glassy appearance of other oral mucosa, especially palate;

8) tongue lobulated/fissured;

9) active or recently restored (last 6 months) cervical caries (>2 teeth); and

10) debris on palate (excluding under dentures).

Self-reported weekly smoking/ EC usage

Participants will be asked (on a weekly basis) to recall how many conventional cigarettes/day they smoked and also how many days out of the previous 7 they used an EC. This data will be collected in several ways based on participant's preference. Participants

with access to a smart phone will be send a weekly text message with an embedded link to a mobile web page with a brief questionnaire, using Qualtrics software. Alternative methods will be available such as email, telephone calls or a hand written diary.

Expired air Carbon Monoxide

In accordance with national guidelines (West, 2005), the study will measure eCO on all participants at 4-weeks and 6-months. A calibrated carbon monoxide monitor will be used.

Participants that withdraw from the study would be followed up at 4-weeks and 6-months unless they did not wish to be contacted.

Salivary Cotinine (SC) and Salivary Anabasine (SA)

Cotinine is a metabolite of nicotine and salivary cotinine is a biomarker of nicotine exposure and will give high readings in those using burnt tobacco, e-cigarettes or other nicotine replacement products. A reading below 15ng/ml signifies a non-user of burnt tobacco or nicotine products (West et al, 2005). Salivary Anabasine (<0.1ng/ml) can be used to confirm if a participant using NRT/EC has also obtained nicotine from nicotine from tobacco (Jacob et al, 2002; Brown et al, 2014). This will allow verification of self-reported smoking status of those who have abstained from all nicotine, those using only NRT/ EC and those still smoking.

Fagerstrom Test for Nicotine Dependence (FTND)

This tool assesses the degree of dependence among smokers coming to a smoking cessation clinic and is extensively used in tobacco research (Heatherton & Kozlowski, 1991). It consists of a set of six questions, giving a score of 0-10 with higher scores representing heavier smokers.

1.	How soon after you wake up do you smoke your first cigarette? *(Circle one response)*	Within 5 minutes 6-30 minutes 31-60 minutes More than 60 minutes	3 2 1 0
2.	Do you find it difficult to stop smoking in no-smoking areas? *(Circle one response)*	No Yes	0 1
3.	Which cigarette would you hate most to give up? *(Circle one response)*	The first of the morning Other	1 0
4.	How many cigarettes per day do you usually smoke? *(Write the number on the line **and** circle one response)*	_____ per day	
		10 or less 11 to 20 21 to 30 31 or more	0 1 2 3
5.	Do you smoke more frequently in the first hours after waking than during the rest of the day? *(Circle one response)*	No Yes	0 1
6.	Do you smoke if you are so ill that you are in bed most of the day? *(Circle one response)*	No Yes	0 1

Mood and Physical Symptoms Scale (MPSS)

This 12-item questionnaire assesses cigarette withdrawal symptoms. It has been used for over 30 years with its psychometric properties being assessed by West and Hajek, 2004. To assess the effect of abstinence you can calculate the change from baseline (just prior to stopping smoking) to the post-abstinence follow-up point for items 1. to 7. and 10. to 12., and take the raw scores for items 8 and 9 (NCSCT, 2012). To compare abstinence symptoms under two or more conditions (i.e. the two arms of this study) these scores can be compared or instead the post-abstinence ratings compared using the baseline ratings as covariates (i.e. instead of subtracting them). This method gives slightly more power to detect differences. The ratings will be analysed individually but also totalled together to give a composite score (MPPS Total).

Microbiological outcome measure

Each participant will have the sub-gingival plaque collected by inserting sterile endodontic paper points into 10 periodontal pockets (ppd ≥ 5mm) and pooling them in a similar technique to Mason et al, 2014. Samples will be collected at 3 time points (Baseline, 3-months and 6-months) and stored at -80oC. Using commercially available kits DNA will be extracted from samples and sent for next generation sequencing using an external laboratory (Dr Scot Dowd, Shallowater, Texas).

The presence and proportions of bacterial species present will be determined using QIIME software. This will provide insights into the pathogenesis of periodontal disease amongst the study participants and may also potentially identify microbial biomarkers for consideration in the future definitive study.

Inflammatory biomarkers (IB)

Each patient will have two specific periodontal sites identified, before randomisation, which have a baseline PPD of 5-8mm. Gingival crevicular fluid (GCF) will be collected and analysis completed for two highly prevalent inflammatory biomarkers: interleukin (IL)- 1β, and matrix metalloproteinase 8 (MMP-8). GCF will be collected at baseline, 3-months and 6-months.

Oral Health Quality of Life Assessment (OHQoL-UK)

The OHQoL-UK questionnaire (Durham et al, 2013) will give a measurement of oral health related quality of life at two points in the study (baseline and 6-months). The 16 items allow responses in either a positive or negative (bidirectional) manner to a series of statements about the effect of oral health on specific aspects of respondents' daily lives. The responses range from "very bad" (score 1) to "very good" (score 5). Responses are then summed to give a total score, or can also be summed within three sub-domains (physical, social and psychological) as described by McGarth and Bedi, 2002. The lower the score the poorer the OHRQoL.

Theoretical Domains Framework (*TDF*) Participant Interviews

The TDF is based on an integration of the 40 main theories of behaviour (Michie et al, 2005; Cane et al, 2012). An expert approach was used to group explanatory constructs by commonalities in 12 domains which represent broad explanations for behaviour hypothesised by current theory. It ensures a) comprehensiveness, b) ability to connect data to specific relevant theories.

TDF interviews will be conducted with up to 40 participants (pending data saturation) at approximately 4-weeks and 6-months. These participants will be purposefully selected based on nicotine dependence, duration of smoking, male/female and age. We will analyse data using theoretical framework analysis where the domains provide an initial framework for narrative data, but expansion of the initial framework is possible. Additionally individual participant data (such as smoking/ e-cigarette weekly usage data) can be used to stimulate narratives in the interviews in a technique previously described by Kwasnicka et al, 2004.

4.4 Data management

A study file will be maintained. CRFs (case report forms) will be developed for collection of clinical data. Any modification to a written form or source document is to be amended with a single line through the erroneous data, with the correction legibly entered, as well as the initials and date of the person making the correction. Data will be entered into secured databases, password protected on the Newcastle University server. All procedures will be in accordance with GCP. Laboratory experiments (including recording of procedures and data) will be conducted in accordance with Newcastle University's Code of Good Practice in Research. Source documents used to originally record volunteer data will be maintained as part of standard case notes in the Newcastle Dental Hospital. A representative sample (~10%) will be randomly audited and source-verified as the study progresses.

4.5 Statistical methods

As this is a feasibility study the analyses of the data collected will be descriptive, with 95% confidence intervals reported where appropriate. No formal statistical testing will be performed.

The clinical outcomes (e.g. PISA, PESA, PPDs) measured at baseline, 3 months and 6 months will be examined graphically and summarised numerically by appropriate measures of location and spread. The relationship between baseline covariates and the potential future definitive study outcome measures will be explored. Such relationships will inform possible stratification of the randomisation for the future definitive trial. Confidence limits for the estimated standard deviations of key study parameters will be calculated and used in sensitivity analyses for sample size calculations for a future definitive RCT.

Summary of outcome measures

Variable / Outcome	Hypothesis	Outcome measure	Method of analysis
PPD (Pocket Probing Depths)	Improvement occurred	Clinical examination	Descriptive statistics
GI (Gingival Index [Lobene Modified Gingival Index])	Improvement occurred	Clinical examination	
PI (Plaque Index [Silness and Low plaque index])	Improvement occurred	Clinical examination	
CAL (Clinical Attachment Loss)	Improvement occurred	Clinical examination	
BOP (Bleeding on Probing)	Improvement occurred	Clinical examination	
CODS- Clinical Oral Dryness Score	Improvement occurred	Clinical examination	
PESA (Periodontal Epithelial Surface Area)	Improvement occurred	Calculation from CAL and BOP	
PISA (Periodontal Inflammed Surface Area)	Improvement occurred	Calculation from CAL and BOP	
Microbiological outcome measure (Micro)	Improvement occurred	Subgingival plaque samples	
Inflammatory biomarkers (IB): - interleukin (IL)- 1β matrix metalloproteinase 8 (MMP-8)	Improvement occurred	GCF samples	
Oral Health Quality of Life Assessment (OHQoL-UK)	Improvement occurred	Questionnaire	
Cumulative burnt tobacco use	Improvement occurred	Questionnaire and bio-chemically validated	
Cumulative EC use	Improvement occurred	Questionnaire and bio-chemically validated	
Fagerstrom Test for Nicotine Dependence (FTND) Score out of 10.	Improvement occurred	Questionnaire	
Mood and Physical Symptoms Scale (MPSS)	Improvement occurred	Questionnaire	

5 Methods: Monitoring

5.1 Data monitoring

A Trial Oversight Committee (TOC) will be responsible for data monitoring. The TOC will combine the roles of a Trial Steering Committee (TSC) and Data Monitoring Committee (DMC). This has been approved by the sponsor (The Newcastle upon Tyne Hospitals NHS Foundation Trust). The TOC will be an independent group of experts consisting of a

statistician, behavioural change expert and periodontal research expert. They will meet on a nine monthly basis throughout the period of the study.

5.2 Harms

Volunteer safety will be monitored from the time each participant signs an Informed Consent Form until conclusion of the study. Any adverse event, however, that is Serious in the opinion of the investigator is to be followed until resolution.

The Newcastle Joint Research Office Standard Operating Procedure 'Adverse Event Recording and Reporting from non-CTIMP studies' (SOP-JRO-08-002) will be followed.

http://www.newcastlejro.org.uk/wp-content/uploads/2013/02/JRO-08-Adverse-Event-Recording-for-non-CTIMP-V2.pdf

Adverse Events

At the time of enrolment, a medical history will be recorded. At all subsequent time points, adverse deviations from baseline status will be recorded as an Adverse Event. These events will be collected at study visits, by reviewing current medical and dental status with the participant. Additionally, the participant may report adverse events at any time by phone or other means of communication, until conclusion of the study.

Serious Adverse Events

A serious adverse event (SAE) is defined in the ICH Guideline for Good Clinical Practice E6 as any untoward medical occurrence that:

- results in death
- is life-threatening
- requires inpatient hospitalization or prolongation of existing hospitalization
- results in persistent or significant disability/incapacity
- is a congenital anomaly or birth defect.

Procedures for reporting adverse events

Adverse events will be recorded in the case report forms, and an assessment by the Chief Investigator will be made of the relationship of the event to the study (i.e. 'definitely not related', 'probably not related', possibly related', 'probably related', 'definitely related') and of expectedness as per available Reference Safety Information for e-cigarettes. The Chief Investigator will report SAEs to the REC.

Follow-up of Adverse Events

In general, an adverse event that is present at the time of study completion will be designated 'on-going' on the case report form if still present at the time of study completion. However, all serious adverse events or other important medical or dental findings per the opinion of the investigator, if present at the time of study completion, will be followed until resolution, regardless of relatedness to participation in the study.

5.3 Auditing

The NUTH NHS FT will provide auditing for this research study.

6 Ethics and dissemination

6.1 Research ethics approval

A favourable opinion from an NHS Research Ethics Committee (REC) will be sought prior to study commencement. The protocol, site-specific informed consent forms, participant information sheets and recruitment materials, and other requested documents—and any subsequent modifications — also will be reviewed and approved by an NHS REC.

6.2 Protocol amendments

Any modifications to the protocol which may impact on the conduct of the study, potential benefit of the patient or may affect patient safety, including changes of study objectives, study design, patient population, sample sizes, study procedures, or significant administrative aspects will represent a substantial amendment to the protocol. Such amendments will be agreed upon by TOC and sponsor (NUTH NHS FT) and approved by the NHS REC prior to implementation.

Administrative changes of the protocol are minor corrections and/or clarifications that have no effect on the way the study is to be conducted. These administrative changes will represent non-substantial amendments and will be agreed upon by TOC and sponsor and will be documented in a memorandum. The NHS REC will be notified.

6.3 Consent and assent

At the baseline session, study details will be discussed with potential participants and informed consent obtained by good clinical practice (GCP) trained members of the study team, who are delegated to do so on the delegation log. Potential participants will be screened for eligibility during the baseline session. A minimum period of 24 hours will elapse between the provision of study information and gaining informed consent.

6.4 Confidentiality

All study-related information will be stored securely at the study site. All participant information will be stored in locked filing cabinets in restricted access offices. The CRFs will be identified by a coded ID [identification] number only to maintain participant confidentiality. All records that contain names or other personal identifiers, such as informed consent forms, will be stored separately from study records identified by code number. The identity of the participants will be kept confidential to the clinical research team at Newcastle Dental School and Hospital. No information that identifies participants will be transferred outside of Newcastle Upon Tyne NHS Foundation Trust, Newcastle University or Newcastle Clinical Trial Unit. .

6.5 Declaration of interests

No competing interests or conflicts of interest exist for any of the investigators. This study is funded by an NIHR Doctoral Research Fellowship.

6.6 Access to Data

Access to data will be restricted to the research team. In addition the NUTH NHS FT will have access to the data for auditing purposes. This is detailed in the informed consent form.

6.7 Ancillary and post-trial care

The Sponsor will arranged for suitable indemnity concerning negligent harm to be in place for this study. Indemnity will be provided via the NHS Litigation Authority.

6.8 Dissemination policy

The findings of this research will be disseminated locally (at departmental meetings), and nationally and internationally via presentations at research conferences. The results of the research will be written up for submission for publication in peer reviewed national and international journals. It is likely that the findings of this research will be of interest to the general public, and Newcastle University has an established press office for communicating findings of research to the press in an appropriate format.

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8.1 Appendix A- Biological specimens

Saliva samples

Collection:

Saliva samples will be collected at baseline, suggested quit date visit, 4-week visit and 6-month visit. All samples will be obtained at least one hour following the last consumption of food, drink or medication by the participant and at least one hour following the last episode of oral hygiene (toothbrushing, flossing, mouthrinses etc). Samples will be collected at any time during the working day. Participants will be seated in the dental chair, without distraction, noise, or conversation for at least 5 minutes prior to commencing collection. No stimulation of the oral tissues will take place, and the mouth will not be examined during this period. A Salivette® will be labelled with a sample identifier number and date. Participants will be provided with and will follow the following instructions to provide their sample. "While holding the Salivette® at the rim of the suspended insert the stopper should be removed. The swab contained should be placed under the tongue (without using fingers) by tipping up when close to the mouth. Do not swallow and leave swab until it is 'soggy'. This can take up to five minutes. Return swab directly from the mouth without using your fingers into the suspended insert and close firmly with the stopper." The Salivette® will be immediately placed on ice and promptly transferred to the laboratory and placed in the -80ºC freezer.

Laboratory evaluation:

1. Salivary Cotinine and Anabasine (Advanced Bioanalytical Service (ABS) Laboratories, Welwyn Garden City, UK).
2. Exploratory analysis of inflammatory profile (Roswell Park Cancer Institute, Buffalo, US).

Sample storage:

Samples will be stored in -80ºC freezer within the Cell and Molecular Biosciences Laboratory (Newcastle University).

Sample transfer:

Samples will be transferred to ABS Laboratories in one shipment at the end of the study.

Samples will be transferred to Roswell Park in 2-3 batches throughout the study.

A courier service will be used to transfer the samples in accordance with the 'Carriage of Dangerous Goods and Use of Transportable Pressure Equipment regulations'. The samples will be classified as 'Category B' samples.

Use in future studies:

Any leftover material sent to these external laboratories will be destroyed following the analysis have been completed.

Informed consent will be gained from participants to retain the samples within Newcastle University for use in future research studies.

Gingival Crevicular Fluid Samples

Collection: GCF samples will be collected at 3 time points (Baseline [visit 1], 3-months [visit 5] and 6-months [6 months]). Two periodontal pockets (ppd 5-8mm) should be identified and recorded in the CRF. The test sites will be isolated using cotton rolls. Any supragingival plaque should be removed with curettes and cotton pellets. Prior to collecting the GCF two pre-labelled cryovials are prepared chairside. A Periopaper strip should be placed carefully into the sulcus of the identified site until mild resistance is felt. The strip is left in place holding the cheek retracted for 30 seconds. The strips should be immediately transferred to separate sterile, dry labelled microcentrifuge tubes. Any excessively blood-soaked strips should be discarded and new samples taken. The samples should be stored on ice before prompt transfer to storage at -80ºC.

Laboratory Evaluation:

1. Analysis for two inflammatory biomarkers: interleukin (IL)- 1β and matrix metalloproteinase 8 (MMP-8) (Newcastle University).
2. Exploratory analysis of inflammatory profile (Roswell Park Cancer Institute, Buffalo, US).

Samples storage:

Samples will be stored in -80ºC freezer within the Cell and Molecular Biosciences Laboratory (Newcastle University).

Sample transfer:

Samples will be transferred to Roswell Park in 2-3 batches throughout the study.

A courier service will be used to transfer the samples in accordance with the 'Carriage of Dangerous Goods and Use of Transportable Pressure Equipment regulations'. The samples will be classified as 'Category B' samples.

Use in future studies:

Any leftover material sent to Roswell Park will be destroyed following the analysis have been completed.

Informed consent will be gained from participants to retain the samples within Newcastle University for use in future research studies.

Appendix S Interview schedule for TDF interview

Interview schedule for TDF interview.

Interview to be held within one month of periodontal intervention/ suggested quit date. Blue text is for e-cigarette group only.

Thank you for agreeing to be interviewed. We are interested in what people think about quitting smoking and what they think about the advice given by a dentist. We are also interested on your views of being provided with an e-cigarette. I would like to ask you some questions about this, which are divided into 11 sections.

When we talk about smoking we are referring to any type of tobacco smoking including cigarettes, roll ups, cigars and pipes.

There are no right or wrong answers; we are interested in all types of views about quitting smoking. If I ask you a question you haven't thought about feel free to take a few minutes to think about it. If you would rather not answer the question that is no problem, we will move on.

Although I'm your dentist, please think of me as a researcher during this interview. There is no pressure here and there will be no influence on your treatment. You are the expert and we are trying to learn from you.

Firstly I wanted to confirm your circumstances with regards to smoking.

1. Are you smoking at the moment?
2. Have you managed to quit at all (previously)?
3. What techniques did you use to try to quit/cut down?
4. Were you given an e-cigarette in this study? Are you using the e-cigarette?

Thinking about your current smoking situation, I am now going to ask you some specific questions about have you have managed to quit/cut down or plan to do so. I am really interested in how you think the dental advice and support plays a role...

Beliefs about capabilities

1. Can you tell me how easy it is for you to quit/cut down at the moment?
2. What have you encountered that makes it difficult, if anything?
3. What would or has helped you overcome these difficulties?
4. On the other hand what have you encountered that makes it easy, if anything?
5. In what way has X helped?

Prompts about dental intervention

6. Did the advice/support provided by the dentist make it easier or more difficult to quit/cut down?

Knowledge

1. What do you know about the techniques for quitting smoking? + views?

Beliefs about consequences

1. What would you say are the advantages of quitting smoking?

2. What would you say are the disadvantages of quitting smoking?

3. Would you say the advantages outweigh the disadvantages?

Prompt about dental intervention:

4. Do you see these advantages or disadvantages of quitting smoking differently after speaking to the dentist?

Social influences

1. What do you think your family and friends think of you quitting smoking/ trying to quit? Would you say this influences you?

2. Generally how many people (same sex and age) do you think smoke?

3. Would you say this influences what you do?

4. Do you have someone who encourages or supports you to quit smoking? How do they encourage/support you?

5. What did your family and friends think about you using an e-cigarette? Does this influence you?

6. Do you know anyone who uses an e-cigarette? Do you think this is socially acceptable/normal?

7. Would you say this influenced you?

Environmental context & resources

1. Where do you usually smoke?

2. Is there anything in your surroundings that have helped you quit/cut down?

3. On the other hand, is there anything about your surroundings that have stopped you from quitting/ cutting down?

3. How does the cost of smoking influence your desire to quit/ cut down?

4. Have you found it easy/ acceptable to use the e-cigarette in your environments?

You were provided with an e-cigarette starter kit for free. You will soon need to start buying your own e-liquid.

5. How has the provision of a free starter kit influenced your ability to quit/ cut down?

6. What do you think about having to buy your own e-liquid in the future?

7. What are you views on the flavourings available?

8. What did you find the most attractive flavour?

9. Did your views on the best flavour change over time/ as you used the e-cigarette.

Motivation & goals

1. How motivated are you to … quit/ cut down/ remain abstinent?

2. What would you say is your main motivation to quit/ cut down/ remain abstinent?

3. Are there any other things that you like or need to do that get in the way of quitting/ cut down/ remain abstinent?

4. Did the provision of the e-cigarette affect your motivation to quit or cut down?

Prompt about dental intervention

5. Can you see your motivation levels changing after your recent dental treatment and the advice given by the dentist? If so, in what way will it change?

Behavioural regulation

1. Can you tell me about any strategies you used to quit/ cut down?

2. Have you made any changes to your daily routine during the quitting attempt?

Memory, attention and decision processes

1. For how much time during the day do you think about smoking?

2. Is there anything that distracts you and makes it easier not to smoke?

3. Has using the e-cigarette become part of your normal routine now? Do you spend much time thinking about it?

You have recently had some dental treatment

3. For how much time during the day do you think about your periodontitis?

Emotions

1. Can you tell me what your mood is like after quitting/ cutting down/ using the e-cigarette? Has this changed?

2. Does your mood influence your smoking habit?

You have recently had some dental treatment

4. Do you think the recent dental treatment affected your mood?

Social or professional role/identity

1. Would you say that being a smoker is part of your personality or who you are?

2. Since you have quit/ cut down have you found any changes to your social interactions?

3. Would you say using an e-cigarette has fitted into your personality or who you are?

4. Since you have been using the e-cigarette have you found any changes to your social interactions?

Skills

1. At the moment, would you say there are any skills you would like to learn that would help you to help you quit/ cut down/ stay abstinent?

Thank you very much, that is all my questions. But is there anything else you would like to add that we maybe haven't covered?

Thanks again for your time.

Appendix T COREQ checklist

COREQ (COnsolidated criteria for REporting Qualitative research) Checklist

A checklist of items that should be included in reports of qualitative research. You must report the page number in your manuscript where you consider each of the items listed in this checklist. If you have not included this information, either revise your manuscript accordingly before submitting or note N/A.

Topic	Item No.	Guide Questions/Description	Reported on Page No.
Domain 1: Research team and reflexivity			
Personal characteristics			
Interviewer/facilitator	1	Which author/s conducted the interview or focus group?	4.3.4
Credentials	2	What were the researcher's credentials? E.g. PhD, MD	4.3.4
Occupation	3	What was their occupation at the time of the study?	4.3.4
Gender	4	Was the researcher male or female?	4.3.4
Experience and training	5	What experience or training did the researcher have?	4.3.4
Relationship with participants			
Relationship established	6	Was a relationship established prior to study commencement?	4.3.4
Participant knowledge of the interviewer	7	What did the participants know about the researcher? e.g. personal goals, reasons for doing the research	4.3.4
Interviewer characteristics	8	What characteristics were reported about the inter viewer/facilitator? e.g. Bias, assumptions, reasons and interests in the research topic	4.3.4, 6.4.1
Domain 2: Study design			
Theoretical framework			
Methodological orientation and Theory	9	What methodological orientation was stated to underpin the study? e.g. grounded theory, discourse analysis, ethnography, phenomenology, content analysis	4.2, 4.3.1
Participant selection			
Sampling	10	How were participants selected? e.g. purposive, convenience, consecutive, snowball	4.3.2
Method of approach	11	How were participants approached? e.g. face-to-face, telephone, mail, email	4.3.2
Sample size	12	How many participants were in the study?	4.3.2
Non-participation	13	How many people refused to participate or dropped out? Reasons?	4.3.2
Setting			
Setting of data collection	14	Where was the data collected? e.g. home, clinic, workplace	4.3.4
Presence of non-participants	15	Was anyone else present besides the participants and researchers?	4.3.4
Description of sample	16	What are the important characteristics of the sample? e.g. demographic data, date	4.3.4, 4.4.1
Data collection			
Interview guide	17	Were questions, prompts, guides provided by the authors? Was it pilot tested?	4.3.3
Repeat interviews	18	Were repeat inter views carried out? If yes, how many?	4.3.4, 4.4.1
Audio/visual recording	19	Did the research use audio or visual recording to collect the data?	4.3.5
Field notes	20	Were field notes made during and/or after the inter view or focus group?	4.3.5
Duration	21	What was the duration of the inter views or focus group?	4.4.1
Data saturation	22	Was data saturation discussed?	4.3.5
Transcripts returned	23	Were transcripts returned to participants for comment and/or	4.3.5

Topic	Item No.	Guide Questions/Description	Reported on Page No.
		correction?	
Domain 3: analysis and findings			
Data analysis			
Number of data coders	24	How many data coders coded the data?	4.3.5
Description of the coding tree	25	Did authors provide a description of the coding tree?	Figure 4.1
Derivation of themes	26	Were themes identified in advance or derived from the data?	4.3.5
Software	27	What software, if applicable, was used to manage the data?	4.3.5
Participant checking	28	Did participants provide feedback on the findings?	4.3.5
Reporting			
Quotations presented	29	Were participant quotations presented to illustrate the themes/findings? Was each quotation identified? e.g. participant number	4.4
Data and findings consistent	30	Was there consistency between the data presented and the findings?	4.4
Clarity of major themes	31	Were major themes clearly presented in the findings?	4.4
Clarity of minor themes	32	Is there a description of diverse cases or discussion of minor themes?	4.4

Developed from: Tong A, Sainsbury P, Craig J. Consolidated criteria for reporting qualitative research (COREQ): a 32-item checklist for interviews and focus groups. *International Journal for Quality in Health Care*. 2007. Volume 19, Number 6: pp. 349 – 357

Appendix U Supplementary quotes

Quote	Participant details	Domains	Themes
Yeah, especially my lass, she thinks it's good [cutting down], she hates us smoking.	Male, 35 years, 40 cigs/day	Social influences	Influence of family members and friends
My husband … he's never ever smoked in his life. Ever. So, I've just spoken to him then, and he was like, "I'm really proud of you", and I was like, "Thank you".	Female, 35 years, 10 cigs/day	Social influences	Influence of family members and friends
If I'm going to be a grandmother, you know, I don't want to be a grandmother that's got a fag hanging out of the side of her gob [mouth]. You know, I want, you know, I want to be able to have a little bit of money to spend on me grandchildren.	Female, 52 years, 15 cigs/day	Social influences	Influence of family members and friends
...they [son and daughter] would love us to stop, they don't smoke, they hate it. Me [my] son's always like, he was really enthusiastic about us coming here...	Female, 49 years, 15 cigs/day	Social influences	Influence of family members and friends

Quote	Participant details	Domains	Themes
And I never used to walk about, say Durham, smoking or anything like that. I don't know, it's just our lass has always said it doesn't look very, nice and so I've never done it really.	Male, 36 years, 15 cigs/day	Social influences	Social pressure
I generally wouldn't smoke, as in, in "public", if you know what I mean	Female, 47 years,10 cigs/day	Social influences	Social pressure
If I went out shopping, you know to the Metro, or something, I probably wouldn't smoke as many because, I find it embarrassing…..I just don't think it looks very attractive….. I think you just got used to going outside, yeah it was a bit of a pain... ...but you'd just end up accepting that. You're the leper and you have to go outside now.	Female, 35 years, 10 cigs/day	Social influences	Social pressure
I don't like walking down the street pushing a buggy having a cigarette you know what I mean?.... I don't know, you kind of feel a bit of a leper, it's already when you smoke it's like, I don't know. No I just, don't want to anymore like.	Female, 31 years, 30 cigs/day	Social influences	Social pressure

Quote	Participant details	Domains	Themes
…you feel like a pariah stood outside smoking.	Male, 59 years, 30 cigs/day	Social influences	Social pressure
…because of the way I'm smoking, I am a secret smoker as well to some people.	Male, 38 years, 10 cigs/day	Social/professional role and identity	Identity- secret smoking
I just never thought that was for me [stop smoking medications], really… just a couple of comments [from] people saying you have queer [strange] dreams and stuff like that, and side effects whatever	Male, 36 years, 15 cigs/day)	Knowledge	Experiences/perceptions of stop smoking medications
Well I'm aware of the chewing gum, I wouldn't fancy that….. I don't like the idea of it. In my mind is mouth cancer and all that sort of thing, you know, chewing baccy and that, I'm aware. Probably doesn't, but, you know, there is [are] other ways to do it so.	Male, 44 years, 30 cigs/day	Knowledge	Experiences/perceptions of stop smoking medications
…[others] said it was amazing. However, they did say the sleep, was horrific. You just feel constantly unsettled, and I don't know whether I, does it, is it supposedly you just how you taste things and... And I don't know how I feel about, almost brainwashing yourself.	Female, 37 years, 30 cigs/day	Knowledge	Experiences/perceptions of stop smoking medications

Quote	Participant details	Domains	Themes
I suffer from depression… Me doctor refused us [me] them, but me [my] Dad took them and he, turned into a real horrible man.	Female, 40 years, 25 cigs/day	Knowledge	Experiences/perceptions of stop smoking medications
I work on, I do driveways and that so, it's like, wherever you want to smoke sort of thing you know… Aye [yes], there's no smoking restrictions at work, at all.	Male, 35 years, 40 cigs/day	Environmental context and resources	Influence of the workplace
…'Cos, my partner that I work with, he smokes. And I'm finding that really difficult…. You know? Especially when I'm having a really stressful night.	Female, 49 years, 20 cigs/day	Environmental context and resources	Influence of the workplace
And then when I'm working it's pretty stressful, you know, on the bridge of a ship or barges and stuff like that. And I can be smoking one after the other really.	Male, 59 years, 30 cigs/day	Environmental context and resources	Influence of the workplace

Quote	Participant details	Domains	Themes
Big. Big, cost… If I work, 12 hours a day, which is my normal working shift, then I would buy, 40 [cigarettes].	Female, 60 years, 15 cigs/day)	Environmental context and resources	Resources of smoking
I don't really pay that much… I've got friends that go to France every so often so I get them pretty cheap.	Female, 43 years, 20 cigs/day	Environmental context and resources	Resources of smoking
I know a lot is made of the financial side of it. I'm personally, it sounds silly, rolling tobacco is a lot cheaper than buying ready-made cigarettes… I go abroad on motorbikes several times a year, so I don't pay a lot for my tobacco… And, I'm fortunate enough that I have a sufficient income that it's not really an issue.	Male, 56 years, 20 cigs/day	Environmental context and resources	Resources of smoking
If and when I'm working it's really, well, some companies I work with you get it free. Cigarettes. And beer. But I don't take the beer.	Male, 59 years, 30 cigs/day	Environmental context and resources	Resources of smoking

Quote	Participant details	Domains	Themes
So, I know the government saying like, "Pack in, pack in", but they're not making it easy for people.	Male, 40 years, 30 cigs/day	Environmental context and resources	Resentment towards authority
...you get stressed, you smoke more.	Female, 43 years, 20 cigs/day	Emotions	Stress management
I suppose if you're having a really bad day. When everything goes wrong from the moment you get up, and you end up in a foul mood. [laughs] Then I tend to smoke a little bit more. I'll be more inclined to smoke, shall we say.	Male, 56 years, 20 cigs/day	Emotions	Stress management
Oh, I've, well I'm in the middle of trying to sell me house and buy a new one, and that's going pear shaped at the minute… Then I've had problems with a member of staff... so, quite, yeah, quite a lot of stuff going on... so unfortunately, I'm probably back on me 10 [cigarettes] a day again.	Female, 47 years, 15 cigs/day	Emotions	Stress management
I've just gone through a difficult split.....so, that hasn't helped at all.	Female, 58 years, 15 cigs/day	Emotions	Stress management

Quote	Participant details	Domains	Themes
And like I say, when I went, I just had to go and buy some tobacco, and when I rolled a one up and smoked it, I felt great. I mean I really, really did.	Male, 59 years, 30 cigs/day	Emotions	Pleasure of smoking
I suppose, in a way for me the relaxation side of it…. You're doing something, be it work as in work, or maybe stuff at home, decorating or whatever…. Or at the end of the day. This evening, Friday, I always celebrate Friday. So, I'll get home this evening, put some music on, open a bottle of beer and have a cigarette. And it's part and parcel of that, if you know what I mean.	Male, 56 years, 20 cigs/day	Emotions	Pleasure of smoking
… the thing is, I enjoy smoking when I've had a meal.	Female, 38 years, 10 cigs/day	Emotions	Pleasure of smoking
You have a fear. You know like a fear of stop smoking. It's, you know, like, I don't know, like I'll keep saying to myself, nothing's going to happen to us if I stop smoking, do you know what I mean?	Female, 58 years, 15 cigs/day	Emotions	Fear of quitting
… I do it out of habit…. I don't actually think I need one.	Female, 25 years, 15 cigs/day	Nature of the behaviour	Habitual nature

Quote	Participant details	Domains	Themes
...I tend to smoke more, when I'm having a drink. Which is typical I would guess.	Male, 55 years, 15 cigs/day	Nature of the behaviour	Link to other behaviours
But that is in the situation of being in a pub when you're drinking as well. That kind of, beer, cigarette thing.	Male, 59 years, 30 cigs/day	Nature of the behaviour	Link to other behaviours
I don't want to go out drinking anytime soon, 'cos I think that's the biggest pitfall for it.	Male, 27 years, 15 cigs/day	Nature of the behaviour	Link to other behaviours
I know it sounds stupid but, for all that I enjoyed a cigarette....I don't like the smell of it, I don't.....I don't actually like, the actual, smell and the taste that it gives you.....but I still, smoked...	Female, 35 years, 10 cigs/day	Nature of the behaviour	Smell
I'm aware that I will be smelling of cigarettes, you know, I was very aware of it when I stopped smoking. It's not a pleasant smell, you know.	Male, 40 years, 30 cigs/day	Nature of the behaviour	Smell
And there's the risk of cancer. But, again, I think I'm on the, I've got this idea in me [my] head that I'm going to be an outlier as far as cancer, getting cancer goes because there's, um, my grandparents smoked a ridiculous amount and	Male, 55 years, 15 cigs/day	Beliefs about consequences	Health

Quote	Participant details	Domains	Themes
they lived well into their 80s. My Grandfather, used to smoke Capstan full strength, one after the other, he would smoke down to that, and then light the next one up, and his fingers were black, with nicotine... but that's a false idea that, there's no evidence for that. That's just an idea I have.			
I might not be a very nice person… And I might put on weight… And that scares me.	Female, 35 years, 10 cigs/day	Beliefs about consequences	Health
I don't think about smoking affecting my teeth area so I don't expect the dentist to be like "Right, this is what smoking's doing, you need, help to cut down"...	Female, 29 years, 10 cigs/day		Dentist-delivered SCA: opportunistic nature
… I think it kind of hit me a bit like, like a brick.	Female, 38 years, 10 cigs/day		Dentist-delivered SCA: opportunistic nature
You know, if I hadn't had all of this carry on I would have just, continued…. But it's really made us stop and think.	Female, 49 years, 20 cigs/day		Dentist-delivered SCA: opportunistic nature

Quote	Participant details	Domains	Themes
Where, you've actually, it's almost, not took it out of my hands, but you've instigated it, by saying, "Look, I'm going to refer you to the group". They've been in touch, then I've been in touch, whereas, would I ever have got round to going… So it's kind of set the ball rolling.	Female, 37 years, 30 cigs/day		Dentist-delivered SCA: opportunistic nature
…that's what scared me, because I think, your teeth are your personality aren't they? They're everything about you.	Male, 59 years, 30 cigs/day		Dentist-delivered SCA: personal context and tangible prompts
… it has made me think, "Crikey, right", and because you have been willing to give me that sort of help and push then yeah, it's, I think it's a good thing sort of having your dentist say, "Look, this is what can, this is what's happening"	Male, 45 years, 15 cigs/day		Dentist-delivered SCA: personal context and tangible prompts
I didn't think that me gums were as bad as what they were, and I have lost that much bone and that much gum, I was quite surprised, in fact I was horrified, 'cos I still think that I've got reasonably, nice teeth, on the whole, and I did look after me teeth... but I obviously, got the shock of me [my] life when you showed us how much of the gum and the bone that I had actually lost. And	Female, 52 years, 15 cigs/day		Dentist-delivered SCA: personal context and tangible prompts

Quote	Participant details	Domains	Themes
that's made us really, sit [up], because again, I can see it, you know what I mean? And it's not until it gets pointed out to you that it's, oh God. Yeah.			
That was, yeah, that hit home. Because like I was saying, you do think, "Oh, it's not that bad", however, when you see the evidence in front of ya [you] ...and it is scary. And you just think, "Oh my word"… so from the visual point of view and the talking through it, because as a smoker, you hear it all the time and it's almost, like doesn't, it's water off a ducks back. "Yeah, yeah, smoking's bad, I get it". But when you see the evidence like that, and it kind of instigated me to do a bit more research myself...	Female, 37 years, 30 cigs/day		Dentist-delivered SCA: personal context and tangible prompts
… when you showed us the X-Ray of me teeth, and everything, I thought, "Listen, I'm going to have to do something really".	Male, 40 years, 30 cigs/day		Dentist-delivered SCA: personal context and tangible prompts
… you see it [health warnings] on the cigarette packets and you think, "Is it scare tactics", you just don't know and like I say, I didn't realise how bad, me [my] gums were until I've had all me [my] measurements done.	Female, 40 years, 25 cigs/day		Dentist-delivered SCA: personal context and tangible prompts

Quote	Participant details	Domains	Themes
…I am conscious of the problem, and the fact that something is being done. You know, you're spending your time, your colleague's spending your [their] time. So, someone is helping you, something is being done to help a problem, it's a positive side, if that makes sense.	Male, 56 years, 20 cigs/day		Dentist-delivered SCA: positive context of quit attempt
It's just knowing that it's going to really help your gums a lot by stopping.	Male, 36 years, 15 cigs/day		Dentist-delivered SCA: positive context of quit attempt
But, I think the possibility of seeing the damage that's done, and the possibility, of it stopping in its tracks.	Female, 37 years, 30 cigs/day		Dentist-delivered SCA: positive context of quit attempt
Now. I feel as though I'm giving myself, the best chance that I can possibly give myself, to reduce the... the impact of gum disease by stopping smoking now.	Female, 52 years, 15 cigs/day		Dentist-delivered SCA: positive context of quit attempt

Quote	Participant details	Domains	Themes
… it is the golden opportunity, you're almost starting from scratch, you're getting the best clean you're ever going to get… And what an opportunity to waste, to be starting and with such good dental treatment, to then reverse all of that like with the smoking.	Female, 37 years, 30 cigs/day		Dentist-delivered SCA: positive context of quit attempt
I think you's [you've] have pushed us into it. It's like it's always been there in the back of me [my] mind I need to do it, but like now, as I'm saying it's like, getting them done and, having me [my] dental work done it's boosted my self-confidence, it's made me feel better about myself, and it's making me want to stop, so...	Female, 31 years, 30 cigs/day		Dentist-delivered SCA: positive context of quit attempt
…I didn't realise, I knew me teeth were really bad. I knew they were really bad and that it was going to be kind of bad news, but I don't think the other dentists have really addressed how bad it was with me.	Female, 38 years, 10 cigs/day		Dentist-delivered SCA: lack of previous support
And where if I went to the doctors and it was like, "Do you smoke?" "Yeah", I would come away and I wouldn't think twice, but now with coming here, it does niggle in the back of me [my] mind…. All the time. So I do think, from	Female, 47 years, 15 cigs/day		Dentist-delivered SCA: different to doctor-delivered SCA

Quote	Participant details	Domains	Themes
getting advice here, I'll be more inclined to stop then [than] definitely the doctors.			
I've listened more to you than what I would a doctor because a doctor you think "Oh, they just tell you this..." you know, but I think, because a dentist tells you and yet you're telling the person the impact it's going to have, because you don't, I mean me personally, I know I've seen it on cigarette packets, you get gum disease and you think, "Oh, yeah, haven't had it yet, I've smoked all..." But then obviously, over time you think, "I should have listened" but too late then. So yeah, I do think a dentist has more impact than what a GP would have.	Female, 45 years, 10 cigs/day		Dentist-delivered SCA: different to doctor-delivered SCA
…it's strange, because I'm diabetic I go for checks at my doctors and stuff. And they've sort of mentioned it, and I think because they've, I don't know, maybe because whenever I've gone I've never been in the right mind-set to think, right yeah I'll take their servi- [services], take up their services and help. And I've just sort of gone in and thought, "yeah, yeah, right, whatever"… but I think because I've been having the work here, and I know that you haven't hold [held] me down and said, you know, "Right, OK, come on". But I think	Male, 45 years, 15 cigs/day		Dentist-delivered SCA: different to doctor-delivered SCA

Quote	Participant details	Domains	Themes
because… because your teeth are a lot of your, who you are as well, your whole sort of make up as well, it has made me think, “Crikey, right”			

Appendix V Supplementary quotes: e-cigarettes

Quote	Participant details	Themes
…at least, I think it's four of the lads, where I go to work, they, they all use them… one of the lads is down to three milligram or something like that in his, so, they must be working for him.	Male, 35 years, 40 cigs/day	Influence of other e-cigarette users
Plus I have, a friend of mine who is the same age as me, went to the same school and everything, [and] works offshore. And he used to smoke roll up tobacco, just the same as me. And the next time I seen him, he was off the tobacco and he was on one of these electronic things [e-cigarette]. [He's] Been on it, six month now and he's finished with the tobacco altogether. And he's smoked more than me, more roll-ups… And I was talking to a Danish guy in Osbourne Road on, last Friday, he lives over here now, but he's on an electric cigarette. And, he swears by it, you know, and he's give up the [tobacco] cigarettes totally, and he says, but he can't give up the electronic one…	Male, 59 years, 30 cigs/day	Influence of other e-cigarette users; concerns about addiction to e-cigarettes/nicotine
And I found the cheaper ones, the early versions were really, bad for me, there's no way I could use them, 'cos I, cough, and cough, terrible. But the newer ones, what	Male, 59 years, 30 cigs/day	Previous e-cigarette experiences

Quote	Participant details	Themes
I've had a try of, seem good, seem as though I could really get away with using one, you know, and I'm sure, for sure I would get off the cigarettes. I know that. I know.		
I've tried one but I didn't feel like I got a big enough, like, puff off it.	Female, 25 years, 15 cigs/day	Previous e-cigarette experiences
And the other ones where you've got to press buttons and then after a while it gets a bit fiddley...'cos the refilling the liquid's quite sticky and if you...And that's a bit annoying 'cos the battery runs out every now and again. (talking about non-study e-cigarette)	Male, 57 years, 10 cigs/day	Previous e-cigarette experiences; technical issues
I'm not going to lie, it's [e-cigarettes] not the best flavour...but, I don't want it to taste nice, if that sounds...because I feel like if it tastes nice, I might use it more. And I don't...so I've waited, obviously I've got the nicotine one in and yeah, it's probably not the best taste, but really, do you want to, a fag or a cigarette to taste really nice where you want to keep picking it up...don't want that.	Female, 35 years, 10 cigs/day	Concerns about addiction to e-cigarette/nicotine

Quote	Participant details	Themes
I think the one area, and I have a, almost a caution note, it's the partner of one of the ladies I work with...who, quite a nervous person, and was a very very heavy smoker…40, 50 a day. All his life, I mean really was. About a year and a half ago… [he used an e-cigarette and] he actually has given up smoking. And I think it's tremendous, and within the group, tremendously. But over the past year and a half, his reliance on the e-cigarette, is getting more and more and more…So, initially… a group of us went out for a meal, I went out for a cigarette, he'd come out with me and have a puff, yeah. About three months ago, we went to a wedding reception, he had two e-cigarettes with him, in case the battery went wrong on one or ran out. He was having secretive puffs on it, inside, and then coming out with me as well. So it's almost as though his addiction or habit, had turned.	Male, 56 years, 20 cigs/day	Concerns about addiction to e-cigarette/nicotine
… the last time I had the e-cigarette it was like a learning curve as well, the one that used to leak. 'Cos really it was just permanently hanging out the side of me mouth, and it was like, I'm thinking like, my nicotine level must have gone flying up through the roof because I must have been taking more nicotine, than I would have been if I had've been smoking. So that's why I've decided, this time, when I'm going to do it, I'm going to	Female, 52 years, 15 cigs/day	Previous e-cigarette experience; concerns about addiction to e-cigarettes/nicotine

Quote	Participant details	Themes
actually use me e-cigarette as if it was a cigarette, take a couple of puffs, and then put it down, 'cos that's, what you would do with a cigarette. And then just leave it.		
To be honest I have more social side now...than what I did before. 'Cos when I was smoking, I was getting out of breath easy, and I was like me condition, I cannot walk that far and everything but, I, like I tend, like I can play with me grandchildren more and I'm not getting out of breath, and, it is a real kick home type of thing.	Male, 40 years, 30 cigs/day	Health considerations
He's [husband] alright as long as I go outside. 'Cos he's like, you know, read reports that it hasn't been, fully looked into, what the vape does to people around you. I think there was something flying about Facebook the other day about popcorn lung or something so...he's like, worried that I'm replacing one lung problem with another, but I said, "Well, it's like everything, until everything's been out a few years, you don't know what's going to happen"	Female, 40 years, 25 cigs/day	Health considerations
… if I give up the traditional cigarettes and just got on on a little electronic one, then I would see if I could stop that as well, you	Male, 59 years, 30 cigs/day	Health considerations

Quote	Participant details	Themes
know. 'Cos they're bound to be some kind of health issue with that as well.		
Ah, yeah. There's quite a few people on my street use them…You see them all outside using it... They're everywhere you go… Me Mam [mother] thinks it looks stupid but, it's doing the job so.	Female, 43 years, 20 cigs/day	Social acceptability
I think me, it's probably the e-cigarette is having something to do with my hands. Or having something in my hand which sort of replicates a cigarette.	Male, 45 years, 15 cigs/day	Benefit of behavioural similarities
I think it's because I've got something to hold on to…So, I know it sounds stupid but, I'm getting that like I would get a cigarette.	Female, 35 years, 10 cigs/day	Benefit of behavioural similarities
…the patches and the little inhaler did worked but as I said, I find the e-cig because you're actually seeing the smoke, so psychologically I think it does work better than, this little and plus this little plastic thing doesn't look very good like...	Female, 45 years, 10 cigs/day	Benefit of behavioural similarities

Quote	Participant details	Themes
I think the e-cigarette's really good…I think that's really helped…Because it feels like you're having a cigarette, but you're not. And it gives you the same sort of feeling.	Female, 47 years, 10 cigs/day	Benefit of behavioural similarities
Easier than I thought [quitting tobacco cigarettes]. It was a lot easier. I think it's 'cos you're taking in smoke and you're blowing it out so you feel like you're having a tab…I don't think I would have been able to do it without that…I think it's just 'cos you feel like you're having a tab, 'cos of the smoke…I think it's, you need something in your hand.	Female, 43 years, 20 cigs/day	Benefit of behavioural similarities
…eventually you have to go your own way and it's down to your own determination and what-not. So, I think the amount that you gave us, and the kit that you gave us, was absolutely spot-on.	Female, 52 years, 15 cigs/day	Perceptions of the e-cigarette starter kit
… using it for a week you're going to decide whether it's going to be the right tool for you to stop smoking or not, so, I think two bottles is fair.	Male, 27 years, 15 cigs/day	Perceptions of the e-cigarette starter kit
I've had to buy some more liquid...I'm getting it from, 'cos I wasn't too keen on the minty one, it was very strong...so I've the	Female, 31 years, 30 cigs/day	Perceptions of the e-cigarette starter kit

Quote	Participant details	Themes
Lloyd's chemist...opposite my doctor's has got, all the stuff in, the proper like, same as I'd got, so...		
I know there's lots of shops sell that liquid as well including Boots [pharmacy], I was there yesterday.	Female, 47 years, 10 cigs/day	Perceptions of the e-cigarette starter kit
… I don't live in Newcastle… so I'd ordered online, and it wasn't until I went into Superdrug in Houghton, and they sell...They don't have a massive selection...but they obviously sell the tops [tanks]...and you put the liquid in. So that would be handy. And they do like the starter packs and stuff like that.	Female, 40 years, 25 cigs/day	Perceptions of the e-cigarette starter kit
… but it has had its advantages having two batteries 'cos I always make sure one's on charge and I have it in the car as well so I can charge it in the car...Yeah, so I do think two batteries, if anyone's going to stop it's an advantage. Because when one's on charge you can use the other one obviously.	Female, 45 years, 10 cigs/day	Perceptions of the e-cigarette starter kit
I mean you got the extra battery as well, and I know from Karen at work. She's got about six...all over the three years, 'cos she always said, if she was at work and one ran out...it was like, "Well	Female, 40 years, 25 cigs/day	Perceptions of the e-cigarette starter kit

Quote	Participant details	Themes
what you're going to do, what am I going to do? What am I going to do?" So she's got like a few now, a couple in her work drawer, a couple at home...		
…I think I would just stick to like the fruity ones.	Female, 60 years, 15 cigs/day	Influence of flavour
[Asked if interested in tobacco flavoured e-liquids?] Not really, 'cos when I smoke, I divvent [don't] really like the taste of it anyway, to tell you the truth…I just smoke 'cos I need the nicotine sort of thing, so...the different flavours is actually better. Sort of thing, you know.	Male, 35 years, 40 cigs/day	Influence of flavour
I just thought, Mint [flavoured e-cigarette] would, [laughs] I don't know whether it would refresh my breath or whatever, but I just thought Mint would be nice, yeah.	Female, 47 years, 10 cigs/day	Influence of flavour
[Interested in fruity flavours?] No, No, I tried them when me [my] son had it, and, I cannot. [laughs]…It's just, they taste horrible really. I don't know why, but it's just the taste of it, I cannot get	Male, 40 years, 30 cigs/day	Influence of flavour

Quote	Participant details	Themes
away with it…So I'd rather use the tobacco one and just come down off that...and then it'll be alright.		
Tobacco flavour. I've tried these strawberry and stuff like that and they do nothing for me.	Male, 59 years, 30 cigs/day	Influence of flavour
...and I've just been using the one flavour at the minute which was the Mint. And yeah, I'll probably look at getting that again 'cos I found that nice, I'm not a big fan of Cherry but there wasn't much [choice] so I think I'm going to stick with the mint… I've always smoked with menthol filters as well...and I actually find it quite close to what it was, to be honest with you, similarities to the taste.	Male, 27 years, 15 cigs/day	Influence of flavour
Blended tobacco, I'm still on that…Yeah. It's like, when people pass you and they're blowing out them fruity ones, I, it knocks you sick. I don't like the fruity ones.	Female, 43 years, 20 cigs/day	Influence of flavour
[What were the issues?] It was more getting it turned on…So I was like, "Right, I've got to press it 10 times", so I was like, "Right". So then I was having a drag, then I felt embarrassed	Female, 35 years, 10 cigs/day	Technical issues

Quote	Participant details	Themes
having a... [laughs]…So then, it'd go off, so I couldn't get, I couldn't get a, an actual drag...so I was like, "Right, what am I actually doing? I'm like, trying to get a drag on something that I can't even work", So it just took me a little bit of time just to, I've got to turn it on 10 times...then you listen to like this gargly sound...and then obviously, you can use it…I've got it sussed.		
I must admit me son did say to us the other day, "Oh are you starting to use that [e-cigarette] again, that's really good"… So I was thinking, "Well, yeah", and I think that did help because at the beginning of the week like I said, it give us a bit of a boost…So I really should have him, [laughs] constantly, behind, watching me, yeah.	Female, 47 years, 15 cigs/day	Technical issues
Obviously I've got like, me vapour pen…That's really helped, really, really...I just borrowed it...me son had it, ah-huh. And, he says, "Well you can lend it 'til I get the money to get one"…I says, "Ah, nee bother". And it's been absolutely great… (participant is using their own e-cigarette while in the control group)	Male, 40 years, 30 cigs/day	Technical issues

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