The Impact of Therapeutic Interventions on Quality of Life in the Periodontitis Patient.

Thesis submitted by

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Declaration

'I, Natalie Mui Suan Leow confirm that the work presented in this thesis is my own. Where information has been derived from other sources, I confirm that this has been indicated in the thesis.'

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Natalie M. Leow

31st March 2023

Dated

Abstract

Periodontitis, an inflammatory, chronic multi-factorial disease involving tooth supporting structures, detrimentally affects oral health-related quality of life (OHRQoL). The aims of this PhD were to investigate the impact of therapeutic interventions in the treatment of periodontitis, with emphasis on OHRQoL and quality of life (QoL), utilising patient reported outcome measures (PROMs). A further aim was to evaluate the benefits (or harms) of long-term supportive periodontal care (SPC) regarding clinical and patient-based outcomes.

Three clinical studies assessed PROMs in the treatment of stage III/IV periodontitis. Study 1 assessed non-surgical therapy (NST), triangulating clinical outcomes with OHRQoL and QoL; Study 2 compared [redacted]; and Study 3 compared two treatment approaches (intensive versus control) in a cohort of patients with diabetes. The minimally important difference (MID) was estimated for OHRQoL in the three clinical studies, to ascertain a minimum change in score which might be important for the patient following an intervention. Finally, a systematic review (SR) evaluated the benefits/ harms of long-term SPC.

Study 1 found NST improved clinical outcomes and OHRQoL but not QoL. The triangulation of these outcomes showed that OHRQoL correlated with QoL, but neither correlated with extent of unstable disease (number of probing pocket depths ≥5 mm) following NST. [redacted] Study 3 found in patients with diabetes, OHRQoL and self-rated periodontal health improved at 12-months, regardless of the intervention intensity. MID was found to be in the range of 4.5-5.5 scale points in studies 1 to 3. The SR highlighted the lack

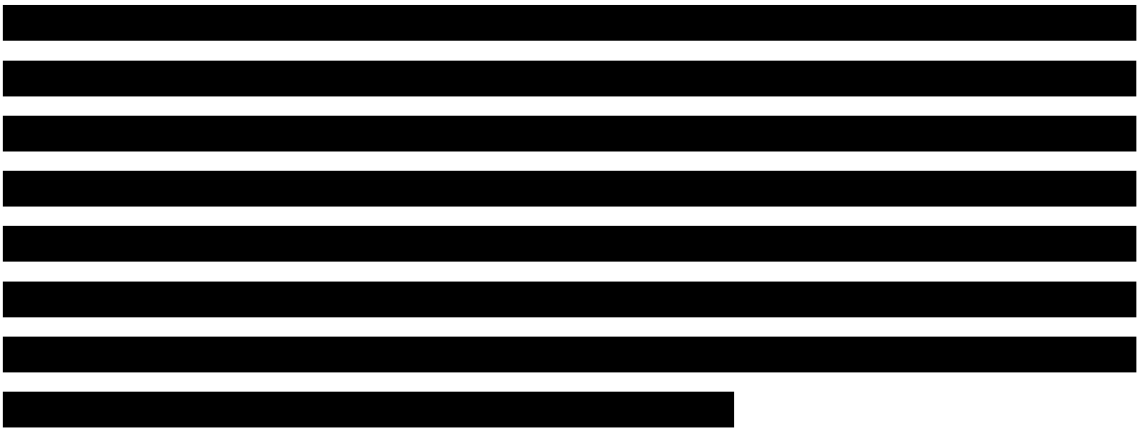
of studies evaluating OHRQoL in long term SPC. Long term regular SPC was beneficial when evaluating tooth and clinical attachment loss (compared with no/ irregular visits).

This PhD provides evidence that treatment of periodontitis results in improved OHRQoL, and patients with co-morbidities (i.e., diabetes) also benefit. Estimation of the MID for the interpretation of OHRQoL, allows stake-holders to better understand how meaningful benefits (or harms) of treatment are to the patient. Further studies using PROMs as a primary outcome are needed to further clarify the impact of other treatment options and impacts in SPC.

Impact Statement

This thesis presents novel evidence which contributes to the scientific knowledge base on OHRQoL and QoL in the treatment of stage III and IV periodontitis, including medically compromised patients (i.e., diabetes mellitus). Rarely seen in the periodontal literature, MIDs were estimated for three different study populations presented in this thesis, following a variety of therapeutic interventions. These MIDs will contribute to existing estimates to gain greater accuracy in determining a more focussed range of MIDs in the treatment of patients with severe periodontitis and is the first estimation for patients with periodontitis living with diabetes. Importantly, greater knowledge of MIDs will influence future clinical research, particularly regarding appropriate sample sizes. This thesis also identifies the need for high-quality clinical trials considering validated measures of OHRQoL (PROMs) as a primary outcome in various phases of the journey of a patient with periodontitis, including those in maintenance care. General QoL does not appear to be affected significantly by periodontal therapies in the patient groups included in this thesis, however studies with larger sample sizes would be necessary to investigate this further, particularly in medically compromised individuals, with the possibility to include cost-effectiveness analyses also.

The cohort study (Chapter 4) contributes to the existing knowledge on OHRQoL and NST in stage III/ IV periodontitis, and takes this further, by attempting to clarify the relationship between both clinical and OHRQoL outcomes to general QoL. This research re-enforces the positive impact of NST in treating periodontitis and can be used to inform policy-makers on the significance and importance of treatment to the patient, to potentially prioritise and direct resources appropriately. General QoL does not appear to be affected by NST in this group of patients, however, is correlated with OHRQoL.



The RCT (Chapter 6) which included patients with diabetes, further re-enforced the positive impact of periodontal treatment in patients negatively affected by other conditions. The study highlighted the benefits of periodontal therapy on metabolic control (HbA1c) but also on OHRQoL. The study not only has the potential to influence and inform on local, national, and international guidelines regarding the management of patients living with diabetes (e.g., prioritise screening and treatment of periodontitis), but also identifies the need for further long-term research on patients with co-morbidities, to ascertain the impact (positive or negative) of periodontal therapy.

The published systematic review and meta-analysis (Leow et al., 2021), a result of Chapter 7, was a core paper used as evidence for the development of the European Federation of Periodontology S3 level, clinical practice guideline for the treatment of stage IV periodontitis (Herrera et al., 2022). This guideline is integral in assisting healthcare professionals in making evidence-based clinical decisions in conjunction with their patients suffering with periodontitis across the world. Furthermore, may be used to influence policies at a variety of levels.

In summary, this thesis contributes further scientific knowledge where gaps currently exist, by helping to inform patients and clinicians in the decision-making process in the management of advanced forms of periodontitis, and confirming the benefits of periodontal interventions on OHRQoL, including in patients living with diabetes. Additionally, QoL does not appear to be affected

following therapeutic interventions in the treatment of stage III/IV periodontitis, however high quality clinical trials are required to confirm or refute these findings. A portion of this dissertation has already provided evidence for the Stage IV European guideline in Periodontology which has far reaching impact world-wide.

Scientific Output

Publications

Leow, N. M., Hussain, Z., Petrie, A., Donos, N. and Needleman, I. G. (2016). Has the quality of reporting in periodontology changed in 14 years? A systematic review. *J Clin Periodontol*, **43**, 833-838. DOI: 10.1111/jcpe.12572

Leow, N. M., Moreno, F., Marletta, D., Hussain, S. B., Almond, N., Needleman, I. (2021). Recurrence and progression of periodontitis and methods of management in long-term care: A systematic review and meta-analysis. *J Clin Periodontol*. DOI: 10.1111/jcpe.13553.

Needleman, I., Almond, N., **Leow, N.**, Phillips, J. Outcomes of periodontal therapy: Strengthening the relevance of research to patients. A co-created review. *Periodontol 2000*. 2023; 00:1- 15. doi:10.1111/prd.12483

Poster Presentations

2021 IADR/AADR/CADR General Session, Virtual. July 2021. 'Treatment of Periodontitis and Patient-Reported Oral Health Outcomes in Diabetes.'

UCL Faculty of Medical Sciences Research Day, London. July 2016. 'Fair test or bias: Are we reporting research transparently?'

Oral Presentations

2018 IADR/PER General Session & Exhibition, Excel London. July 2018. 'Effect of Non-Surgical Periodontal Therapy on Patient-Reported Outcomes Measures. '

UCL Faculty of Medical Sciences, Dean's Research Prize Event & 3 Minute Thesis Competition, London. February 2017. 'Finding the Best Treatment for Gum Disease'.

UCL Eastman Dental Institute, Research Away Day, London. November 2016. 'Patient Reported Outcomes in the Treatment of Periodontitis'.

UCL Eastman Dental Institute, PhD Postgraduate Symposium, London. May 2016. 'The Efficacy of Surgical Modalities in the Treatment of Periodontitis. A Randomised Controlled Trial'.

Acknowledgements

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My appreciation also goes to all present and past students and staff of the Unit of Periodontology and Eastman Clinical Investigation Centre, UCL Eastman Dental Institute, for their roles in providing support, guidance and friendship.

Lastly, I’d like to thank my husband, Theo, and children, Phoebe and Matheos, all of whom have fully supported me during the ups and downs of this entire journey, and without their constant patience, this would not be possible.

UCL Research Paper Declaration Form (for own published work)

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Recurrence and progression of periodontitis and methods of management in long-term care: A systematic review and meta-analysis.

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   Supervisor/ Senior Author (where appropriate)

   Ian Needleman

   *Date **22.12.22***

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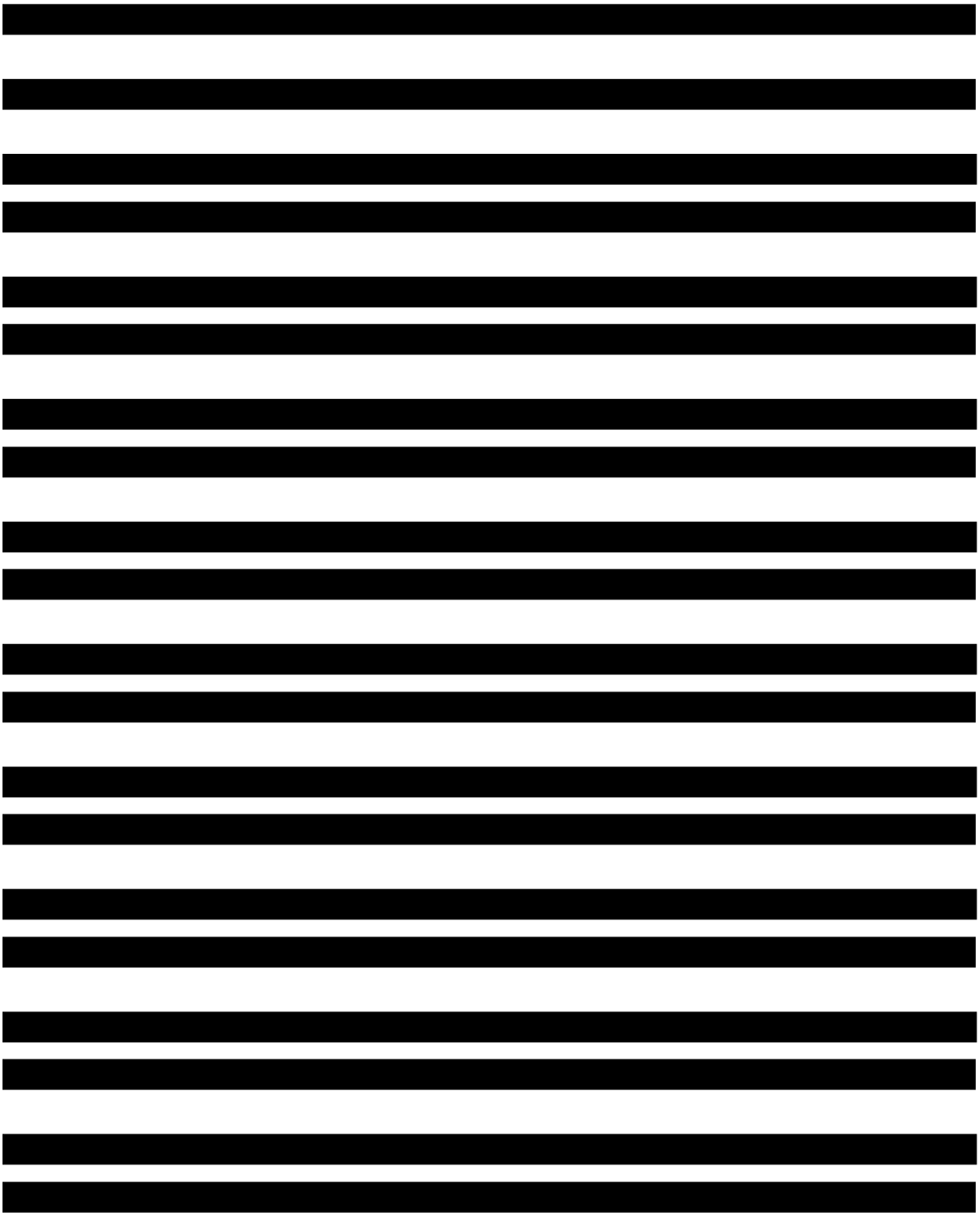

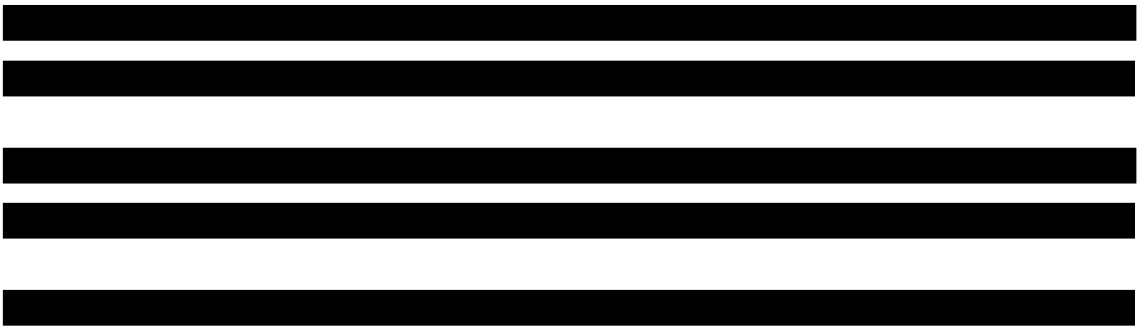

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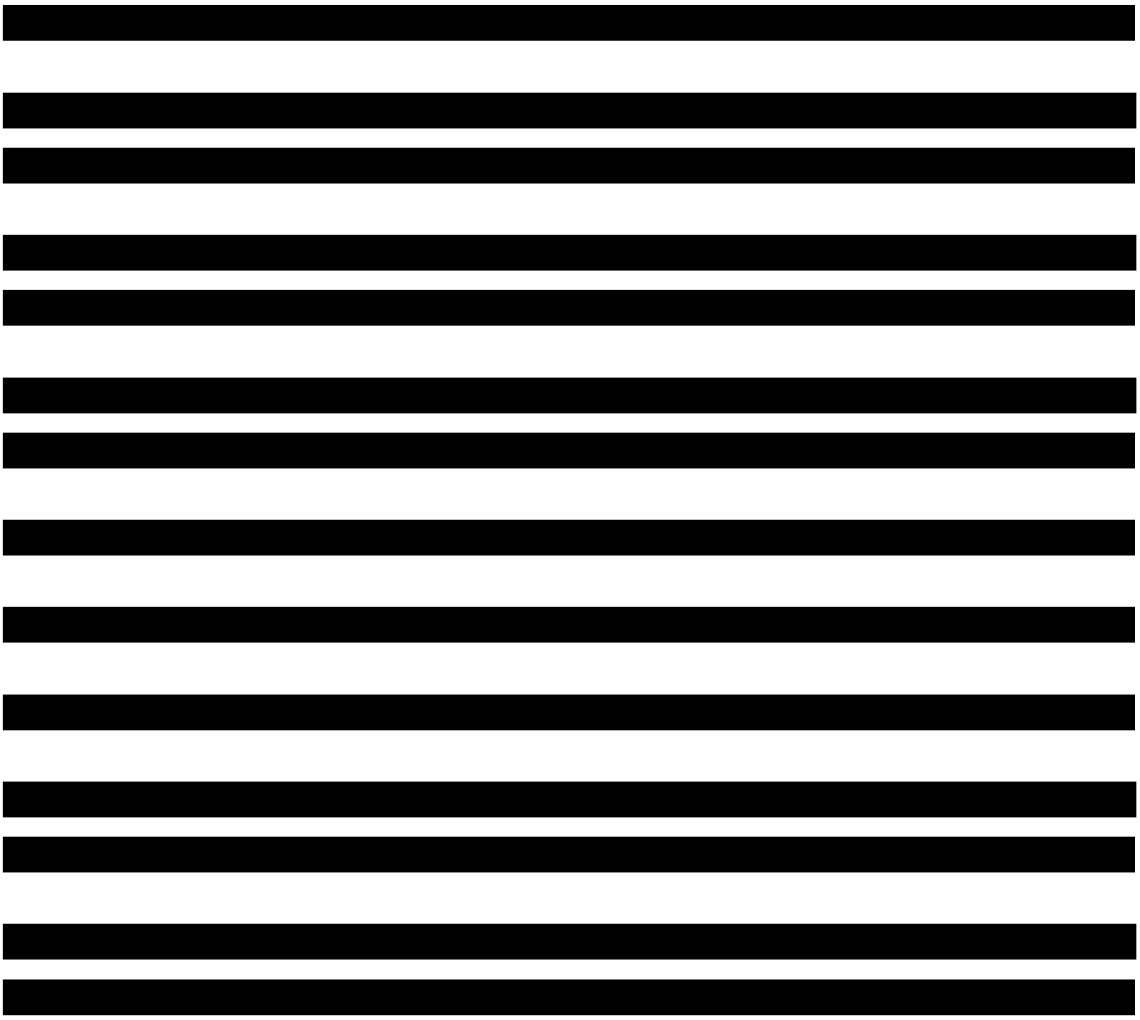

List of Abbreviations

BOP	Bleeding on probing
CAL	Clinical attachment level
CONSORT	Consolidated Standards of Reporting Trials
CONSORT PRO	Consolidated Standards of Reporting Trials Patient Reported Outcome Extension
CPT	Control periodontal treatment
GSROH	Global self-ratings of oral health
HRQoL	Health-related quality of life
IPT	Intensive periodontal treatment
MID	Minimally important difference
NHS	National Health Service
NST	Non-surgical therapy
OHIP-14	Oral health impact profile - 14
OHQoL-UK	Oral health quality of life – United Kingdom
OHRQoL	Oral health-related quality of life
OIDP	Oral impacts on daily performance
PPD	Periodontal probing depth
PREM	Patient-reported experience measure
PRO	Patient-reported outcome

PROM	Patient-reported outcome measure
PROTEUS	Patient-reported outcomes tools, engaging users and stakeholders
REC	Recession
QoL	Quality of life
SPC	Supportive periodontal care
ST	Surgical therapy

List of Appendices

1. INTRODUCTION

Periodontitis is a life-long chronic condition that can have significant negative impacts on an individual's day to day life, most commonly due to tooth loss, compromised aesthetics and difficulty chewing. Management of the disease however is principally based on the evaluation of clinical (surrogate) measures (e.g., periodontal probing depths, clinical attachment levels and bleeding on probing) without consideration of factors which may be of greater importance to the patient. Periodontal clinical outcomes, have the limitation that they do not capture how the patient is affected by the disease or its treatment, and as such often lack relevance and meaning from the patient's point of view. Thus, if outcomes are not easily understood or lack importance to the patient, it may be difficult for a patient to engage with their own care which could have implications in long-term management of their disease.

Standardised questionnaires known as patient reported outcome measures (PROMs), seek to obtain a perspective solely from the patient (without interpretation of a clinician/ researcher), with regard to elements of his/her own health, functioning and quality of life (Williams et al., 2016). The inclusion of PROMs in a variety of areas such as research, clinical practice, and health services management, have become increasingly important to inform on clinical decision making, self-management (often of chronic conditions) and the success of healthcare interventions. Over the last decade, a greater number of studies in periodontal research have included PROMs as an outcome measure, but despite strong recommendations from several prominent professional organisations, PROMs are still not routinely embedded in periodontal clinical trials evaluating efficacy and/or effectiveness of interventions, which has implications on clinical decision-making. Furthermore, researchers have struggled to interpret findings of PROMs in a meaningful way, and although not routinely reported in the periodontal literature, a minimally important difference

(MID) estimation is strongly recommended (Revicki et al., 2008, Tsakos et al., 2010, Tsakos et al., 2012, Masood et al., 2014, Devji et al., 2021), in an attempt to quantify the minimum change in PROM score before and after treatment which would translate to an important and relevant change for the patient (Guyatt et al., 1987, Guyatt et al., 2002).

There is a lack of high quality studies exploring oral health-related quality of life (the impact oral conditions and their treatments have on everyday activities) and different treatment approaches (both non-surgical and surgical) in the treatment of severe cases of periodontitis (stage III and IV) in the long-term (Tonetti et al., 2018). No evidence exists evaluating oral health-related quality of life (OHRQoL) in patients with severe periodontitis whilst living with co-morbidities such as diabetes or patients enrolled in long-term maintenance programmes following treatment for periodontitis. Furthermore, no evidence exists evaluating periodontitis and its therapeutic interventions, on overall quality of life (QoL), which has implications for cost-effectiveness of a treatment, and potential to influence policy-makers to fund treatments with the greatest health benefits for the cost.

This lack of evidence is problematic, as currently, key decisions on clinical care can only be made based on clinical outcomes and perceived benefits to the patient in relation to quality of life. Furthermore, without greater clarity on priorities and preferences of the patient, research outcomes are at risk of remaining inaccessible and irrelevant to those living with the disease.

Therefore, the aims of this research were to;

a) investigate the relationship between non-surgical therapy (NST), surgical therapy (ST), OHRQoL and QoL and;

b) investigate the effect of comprehensive periodontal therapy (NST and ST) in medically compromised patients

c) investigate the effect of long-term supportive periodontal care on OHRQoL

To achieve these aims, the following objectives were formulated:

- to assess the impact of NST on OHRQoL and to elucidate its relationship with QoL through a clinical study.
- to assess the impact of ST on OHRQoL and to elucidate the relationship between both these outcomes with QoL through a randomised clinical trial.
- to assess the impact of both NST and ST on OHRQoL in periodontitis patients with type 2 diabetes mellitus (DM).
- to understand the current state of evidence of OHRQoL in periodontitis patients enrolled in a long-term supportive periodontal care (SPC) programme.

This PhD thesis initially presents a background and literature review of the current evidence of OHRQoL in the context of periodontitis and its treatments. Following this, the results of three clinical intervention trials focussed on stage III/IV periodontitis, are presented. Two of these studies explored the impact of non-surgical and surgical treatment of periodontitis with regard to both OHRQoL and QoL, whilst the third study assessed the same treatment modalities, however in a population with type 2 DM. An estimation of MID was also presented for the three clinical studies. Finally, the findings of a systematic review and meta-analysis to inform on OHRQoL in stage III/IV periodontitis patients enrolled in a SPC programme is presented.

2. BACKGROUND

2.1 Periodontitis

Periodontitis is a chronic and progressive inflammatory disease which affects the supporting structures of the tooth (Papapanou et al., 2018). It can result in a pathologically deepened crevice or space (periodontal pocket) between the gingiva and tooth root, and if left untreated can ultimately lead to tooth loss. It is the sixth most prevalent condition in the world, with severe forms affecting 7-11% of adults worldwide (Kassebaum et al., 2014, Kassebaum et al., 2017), and approximately 15% of adults in the United Kingdom (White et al., 2011).

The leading cause of tooth loss worldwide, periodontitis has been demonstrated, amongst other things, to detrimentally affect an individual's nutrition (due to reduced masticatory function), social and self-confidence, and quality of life (Chapple, 2014, 2015, Chapple et al., 2015, Ferreira et al., 2017, Tonetti et al., 2017b, El Sayed et al., 2019, Economist Intelligence Network, 2021). Furthermore, the direct (e.g., cost of treatment), indirect (e.g., losses related to work or travel) and intangible (e.g., pain, lack of confidence) costs to the patient are significant.

In addition to the impact on individuals, periodontitis can have far-reaching impacts on communities and society as a whole (Economist Intelligence Network, 2021). It is estimated that that the global cost of lost productivity from severe periodontitis is over 50 billion USD/ year (Listl et al., 2015) whilst healthcare systems across Europe struggle to keep up with the economic costs (estimated to range from 18 to 56 billion Euros per year) involved with treating the disease (Economist Intelligence Network, 2021).

2.1.1 Classification and Treatment

The classification of periodontal diseases has changed over the years, with the most recent classification (Tonetti et al., 2018) having engaged a 'staging' (I-IV) and 'grading' (A, B or C) system, with the most severe stages (III and IV) loosely equating to moderate to severe chronic/ aggressive periodontitis in the classification prior (Armitage, 1999). The staging and grading system was introduced to provide a framework for diagnosing, treatment planning and monitoring of periodontitis whilst considering risk factors, severity, and complexity of the disease (Papapanou et al., 2018, Tonetti et al., 2018). Staging is primarily based on the severity and extent of periodontitis, whilst grading is based on factors recognised to influence the disease course and treatment outcomes (i.e., age, smoking, diabetes).

Diagnosis of periodontitis utilises the framework of the classification (Tonetti et al., 2018), together with clinical and radiographic findings. The periodontal pocket is clinically measured using a periodontal probe (probing pocket depth) and is described in millimetres. Periodontal probing pocket depth (PPD) is defined as the distance from the gingival margin to the apical extent of probe tip penetration into the periodontal pocket (Listgarten, 1972, Listgarten, 1980). Along with PPD, other clinical parameters are used to assess and monitor the periodontal status including: clinical attachment level (CAL), gingival recession (REC), bleeding on probing (BOP), evaluation of plaque accumulation and radiographic assessment of the alveolar bone crest (Lang and Tonetti, 1996).

Treatment of periodontitis may be viewed in a *step-wise* manner (Sanz et al., 2020) beginning with guiding behaviour change in the patient. The emphasis in *Step 1* is on risk factor control, re-enforcement of excellent hygiene practices and removal of supragingival deposits. Following an appropriate re-evaluation period, *Step 2* of therapy primarily involves reducing or eliminating the subgingival biofilm/calculus by means of subgingival instrumentation/ non-surgical therapy (NST). The *third step* of therapy addresses those areas which

did not respond favourably to the second step of therapy (i.e., PPD ≥4 mm and bleeding on probing) by means of further NST or surgical therapy (ST), as appropriate. Supportive periodontal care (SPC) may be seen as the final step, whereby the aim is to maintain periodontal stability by monitoring and implementing preventative and therapeutic therapies at regular recall intervals (Sanz et al., 2020).

2.1.2 Risk Factors

Periodontitis is caused by the accumulation of bacteria and their by-products (biofilm) on the tooth, triggering the body's immune response. A microbial dysbiosis occurs within the biofilm (principally keystone pathogens) which signal the release of a cascade of pro-inflammatory cytokines and inflammatory mediators within the soft tissues, to promote tissue destruction (Hajishengallis et al., 2020). The severity of periodontitis can vary according to the extent and duration of the inflammatory response in combination with other modifiable and non-modifiable factors. Once the disease has progressed and supporting tissues destroyed, this can result in a number of symptoms which negatively affects the patient, including tooth migration, hypermobility or loss often leading to masticatory dysfunction and possibly nutritional deficiencies (Tonetti et al., 2017b). Additionally, aesthetics is often compromised, impacting on self-confidence and other aspects of quality of life (Shanbhag et al., 2012, 2015, Buset et al., 2016, Baiju et al., 2017, Wong et al., 2021).

A number of risk factors have been associated with periodontitis which include increasing age, smoking and tobacco use, poor oral hygiene, systemic disease (e.g. diabetes, cardiovascular diseases), genetics, medications, hormones, stress and nutritional deficiencies (Chapple et al., 2013, Tonetti et al., 2017b, Ramseier et al., 2020). Importantly, periodontitis is more prevalent in socioeconomically deprived communities with less access to education and dental services (Kassebaum et al., 2014, Kassebaum et al., 2017).

Diabetes Mellitus

Risk factor control is an essential component of *Step 1* of therapy in the treatment of periodontitis (Sanz et al., 2020) and undoubtedly underpins all subsequent steps of therapy and periodontal maintenance. Smoking and diabetes mellitus are the only recognized risk factors that increase the risk of periodontitis onset and progression, and as such are integral in grading periodontitis (Papapanou et al., 2018, Ramseier et al., 2020). A group of chronic metabolic disorders, diabetes mellitus (DM), is generally experienced as a life-long condition. DM (commonly known as diabetes) is characterised by high blood sugar levels (hyperglycaemia) and occurs as a result of lack of insulin secretion or action, or both (American Diabetes, 2014). A number of mechanisms have been proposed to explain the impaired insulin secretion or sensitivity, some of which include oxidative stress, amyloid deposition in the pancreas and lipotoxicity (Donath and Shoelson, 2011). It's thought that these processes contribute to an inflammatory response and/or are exacerbated by inflammation, and as such, controlling inflammation could be a key factor in reducing or preventing damage.

In 2014, 422 million people across the world (an overall prevalence of 8% of the global population) were diagnosed with type 2 DM (World Health Organization, 2016a). In 2017, it was estimated that over 450 million adults (18- 99 years) were diagnosed with diabetes worldwide, and this is expected to increase to 693 million by 2045 (Cho et al., 2018). In the UK alone, the prevalence of diabetes in 2019 was just over 3.9 million people (Diabetes UK, 2019). The UK National Health Service (NHS) spends at least £10 billion each year on diabetes, and most of this (almost 80%) is spent on the complications of diabetes (Diabetes UK, 2019).

Diabetes is the leading cause of reduced life expectancy and mortality. Complications of hyperglycaemia are experienced on both a macrovascular and microvascular (nerve and endothelial cell damage) scale and can be

devastating. Cardiovascular disease and peripheral vascular disease are macrovascular complications which can ultimately lead to death or amputation, respectively. Retinopathy, nephropathy and neuropathy are common microvascular complications (Verhulst et al., 2019b). The associated negative impact on a patient's quality of life (QoL) is without doubt substantial (Wexler et al., 2006, Trikkalinou et al., 2017, Verhulst et al., 2019a).

Classification of Diabetes Mellitus

Diabetes may be categorised into type 1, type 2 and gestational diabetes, which is helpful to determine therapy. Other specific types of diabetes also occur which can be related to genetic defects in ß-cells or insulin action (American Diabetes, 2014). In practice however, many diabetic individuals don't fit into a single class easily. Features of the main classes are outlined in

Table 1.

Table 1. Diabetes Mellitus Classification [adapted from American Diabetes (2021)].

		Cause	Description
Type 1	Immune-mediated (Majority of Type 1 patients)	Cell-mediated destruction of the ß-cells of the pancreas. Often leads to absolute insulin deficiency.	• 5-10% of those with diabetes • Variable rate of ß-cell destruction. • Patients are rarely obese when presenting with this type of diabetes. • Prone to other autoimmune diseases (e.g., Graves'

			disease, Addison's disease)
	Idiopathic (Minority of Type 1 patients)	No known aetiology.	• Often of African or Asian descent. • Episodic ketoacidosis. • Display varying degrees of insulin deficiency.
Type 2		Loss of insulin secretion by ß-cells and is often combined with a degree of insulin resistance.	• 90-95% of those with diabetes. • Most patients are obese or increased proportion of body fat • Increased risk of developing macrovascular and microvascular complications. • Defective ß-cell function.
Gestational		Most often diagnosed in the second or third trimester of pregnancy.	• Often indicative of underlying ß-cell dysfunction. • Increased risk for development of diabetes later.

Diagnosis of Diabetes Mellitus

Diagnosis of DM has traditionally been based on presentation of common symptoms such as polydipsia, polyuria, unexplained weight loss and blurred vision. This was usually confirmed by means of a random blood glucose/ 2-hour post glucose load of ≥200 mg/dL (≥11.1mmol/l) or a fasting glucose level of ≥126 mg/dL (7.0 mmol/L).

Glycated haemoglobin (HbA1c) is also a commonly used marker of chronic glycaemia and reflects blood glucose levels over an extended period of time (usually 2-3 months). In the last 10 years, the use of HbA1c has been advocated to diagnose diabetes, with a threshold of >6.5%/ >48mmol/mol (International Expert Committee, 2009).

Diabetes Mellitus and Periodontitis

Diabetes and periodontitis are inextricably linked. The association between diabetes and periodontitis is bi-directional (Lalla and Papapanou, 2011, Preshaw et al., 2012) whereby periodontitis has been viewed as the, 'sixth complication', of diabetes (Loe, 1993), and diabetes is a recognised risk factor for periodontitis (Papapanou et al., 2018).

Poorly controlled diabetes increased the risk of developing periodontitis by almost twice (OR 1.85, 95% CI 1.61 - 2.11) according to a recent meta-analysis of 27 epidemiological studies (Zheng et al., 2021). Furthermore, periodontitis in patients living with diabetes was found to be worse in severity (mean difference in probing pocket depth 0.23 mm, 95% CI 0.17- 0.29) when compared with patients with well-controlled diabetes/ healthy individuals. One cross-sectional case-control study (Botero et al., 2012) which included 65 participants with diabetes and 81 participants without diabetes, found over twice the risk of developing periodontitis when compared with participants without diabetes (OR 2.24, 95% CI 1.02-4.93). In contrast to the findings of the meta-analysis

described previously (Zheng et al., 2021), this study did not find that PPD was greater for those participants with diabetes compared with those without, however patients with diabetes whom also smoked did have statistically significantly deeper PPD ($p<0.01$). This study had a number of limitations including a small sample size (convenience sample) and presentation of clinical measures such as PPD as medians (rather than number of PPD greater than a certain threshold), which makes it difficult to determine severity and extent of disease. Furthermore, the population was selected from a university setting, therefore may be susceptible to selection bias. The results of this study appear to be in line with other studies on the topic.

Conversely, emerging evidence indicates an increased risk of diabetes onset in patients with severe periodontitis (Ide et al., 2011, Borgnakke et al., 2013, Miyawaki et al., 2016, Winning et al., 2017). One seven- year prospective cohort study of 5,848 non-diabetic participants (Ide et al., 2011) found a trend toward (although not statistically significant) an increased risk of developing diabetes in participants initially displaying severe periodontitis (hazard ratio = 1.28, 95% CI 0.48-1.86). These findings were re-enforced by a subsequent Japanese cohort study (Miyawaki et al., 2016) of 2,469 male participants that the self-reported symptom of tooth loosening (assumed due to periodontal reasons) was associated with an increased risk (adjusted relative risk = 1.73, 95% CI 1.14- 2.64) of incident type 2 diabetes over a 5 year follow up period. Further to this, a prospective cohort study (Winning et al., 2017)of 1,339 males based in Northern Ireland found similar increased risk (hazard ratio = 1.69, 95% CI 1.06 - 2.69) of developing diabetes (median follow up of 7.8 years) when individuals exhibited moderate to severe periodontitis at baseline. One large cohort study conducted in Japan (Morita et al., 2012) studied 6,125 people with HbA1c <6.5% at baseline and followed them for 5 years. The authors reported the relative risk for increased HbA1c level (≥6.5%) at 5 years was 2.47 ($p=0.122$) for individuals with 4-5mm probing depths at baseline and 3.45 ($p=0.037$) for those with ≥6 mm probing depths at baseline. Similar results had

been demonstrated earlier (Demmer et al., 2008), where data from the National Health and Nutrition Examination Survey (NHANES 1) was evaluated. The study found that from the 9,296 participants (1971-1976 to 1982-1992), those with more severe periodontitis at baseline had an adjusted odds ratio 2.26 (95% CI 1.56-3.27) for developing incipient diabetes. This study however had a number of limitations, firstly, the diagnosis of periodontitis was according to the periodontal index (scoring from 0-8.0) according to clinical observations (e.g., visual inflammation, mobility, PPD at one site) which could over-estimate the severity and extent of disease. Secondly, according to the statistical analysis plan, periodontitis 'cases' were defined in three different ways resulting in multiple statistical analysis and somewhat selective conclusions based on the definition showing the most significant result. Although the available research tends to be from two populations (Japan and the USA), the trend appears to support that patients with severe periodontitis are at greater risk of developing diabetes (Demmer et al., 2008, Borgnakke et al., 2013). This further strengthens the bi-directional relationship of periodontitis and diabetes.

The possible mechanisms to explain the link(s) between periodontitis and diabetes are complex. Common risk factors, such as smoking, obesity, excessive alcohol consumption, age and gender, may make the relationship between the two diseases less clear. Inflammation however, appears to be a key parameter in both diabetes (Tsalamandris et al., 2019) and periodontitis (Preshaw et al., 2012, Hajishengallis et al., 2020). The mechanistic relationship between diabetes and periodontitis (Preshaw et al., 2012, Polak et al., 2020) might be explained in a number of ways. The hyperglycaemic state seen in diabetics can result in activation of inflammatory pathways (Brownlee, 2005), and, non-specific acute-phase proteins of inflammation such as interleukin-6 (IL-6), tumour necrosis factor alpha (TNF-α) and C reactive protein (CRP) are commonly seen in these patients. Patients with periodontitis also exhibit high serum levels of IL-6 and CRP, with the former correlating with severity of disease (Loos, 2005). Thus, diabetes increases inflammation in the periodontal

tissues and the inflammation associated with periodontitis could be sufficient to heighten the diabetic state (Preshaw et al., 2012). Another possible mechanism is regarding the effects of diabetes on the oral microbiome. Although there is a paucity of strong evidence, some studies have indicated that hyperglycaemia favours dysbiosis and alters the composition of oral microorganisms and their metabolites (Xiao et al., 2017, Li et al., 2023). This may be explained by the upregulation of certain cytokines (e.g., IL-17), leading to increased inflammation and changes in the composition of the oral microbiome to become more pathogenic.

Periodontal treatment has been shown to improve diabetic control in a number of randomised controlled trials (Simpson et al., 2022), in patients with predominantly type 2 diabetes. Moderate-certainty evidence from 30 studies, found that following periodontal treatment, an absolute reduction in HbA1c of 0.43%/ 4.7 mmol/mol (95% CI -0.59 to 0.28%/ -6.4 mmol/mol to -3.0 mmol/mol) might be expected at 3-4 months, whilst at 12 months, this reduction could be 0.50%/5.4 mmol/mol (95% CI -0.55% to -0.45%/-6.0 mmol/mol to -4.9 mmol/mol) based on one study of 264 participants (D'Aiuto et al., 2018).

The strength of the evidence has subsequently led to an important, recently updated guidance from the National Institute for Care and Health Excellence (NICE) stating that healthcare practitioners should advise adults with type 2 diabetes that; i) they are higher risk of developing periodontitis and ii) managing periodontitis can improve their blood glucose control and reduce their risk of hyperglycaemia. Additionally, NICE recommends patients with type 2 diabetes to have regular oral healthcare reviews and regular appointments to manage the periodontitis (as appropriate) (National Institute for Health and Care Excellence, 2022b). Prior to this, the NHS commissioning standard (NHS England and NHS Improvement, 2019) for adults with type 2 diabetes, recognised the need for patients with diabetes to access effective oral healthcare services for general and oral health benefits. Furthermore,

economic modelling supports the benefits of treatment of periodontitis, and particularly early intervention and diagnosis (NHS England and NHS Improvement, 2019, Economist Intelligence Network, 2021, National Institute for Health and Care Excellence, 2022b).

Treatment Approaches

The treatment of periodontitis aims to resolve inflammation by reducing the supra- and sub-gingival plaque and calculus and establishing those conditions which favour the maintenance of periodontal health (in conjunction with risk factor management) (The American Academy of Periodontology, 2011, 2015, Sanz et al., 2020). Ideally, the clinician would aim for periodontal pocket resolution (PPD of ≤4mm) and clinical attachment level gain. This is achieved by a first phase of NST where the primary goals are to improve oral hygiene and reduce inflammation by the removal of plaque and calculus from the root surface (Suvan et al., 2020).

Non-Surgical Periodontal Therapy

Non-surgical periodontal therapy is often carried out under local anaesthesia, using a variety of methods including hand instruments, sonic or ultrasonic scalers. Often, NST does not result in complete resolution of the disease. Residual PPDs of 6mm or greater, have been shown to have an increased risk of disease progression (Claffey and Egelberg, 1995, Claffey et al., 1996, Matuliene et al., 2008). Therefore, to promote periodontal stability, residual periodontal pockets may require a subsequent surgical or corrective phase as an adjunct to non-surgical therapy, to provide access and correct or eliminate anatomical variations to enhance long term maintenance of the tooth (Polak et al., 2020, Sanz-Sanchez et al., 2020).

A strong and consistent evidence-base supports the success of NST in the reduction of bleeding on probing (BOP), reduction of PPD and gain in clinical

CAL (Heitz-Mayfield et al., 2002, Suvan et al., 2020). One recent systematic review (Suvan et al., 2020) estimated weighted mean PPD reduction of 1.4mm (95% CI 1.0-1.7) at 6-8 months following NST based on nine randomized controlled trials. Pocket closure (PPD≤4 mm) was estimated at 74% (95% CI 64-85), thus although highly successful, often more treatment is required following NST. It must be acknowledged also that NST is time-consuming, technically demanding and often does not remove all hard deposits (Cobb, 2002), often leading to residual PPD and requiring further treatment, most commonly in the form of surgical therapy.

Periodontal Surgery

The success of surgical approaches in the treatment of periodontitis has long been established (Rosling et al., 1976, Pihlstrom et al., 1983, Kaldahl et al., 1996a, Sanz-Sanchez et al., 2020). Currently however, there is no consensus on the superiority of one surgical technique over another and the indications for applying more resective periodontal surgical procedures which include removal of bone (osseous surgery) remain elusive for the everyday clinician. In part, this uncertainty might be due to generally small studies which could lack adequate power to show differences (if they exist). Furthermore, lack of full reporting of methods limits the potential to combine studies in a meta-analysis, which might otherwise be able to identify differences in data worthy of further investigation (Leow et al., 2016).

Rosling et al. (1976) evaluated the healing capacity of periodontal tissues over a 3 year period by comparing the following surgical techniques: : 1) the apically repositioned flap operation including elimination of bony defects, 2) the apically repositioned flap operation including curettage of bony defects but without removal of bone, 3) the Widman flap technique including elimination of bony defects, 4) the Widman flap technique including curettage of bony defects but without removal of bone, 5) gingivectomy including curettage of the bony defects but without removal of bone. The authors showed that in patients with a

high level of oral hygiene, optimal gingival conditions can be obtained using these surgical approaches. No statistically significant difference was found in regard to pocket reduction, when comparing the various surgical techniques. Additionally, infrabony defects presented the highest amount of bone fill when bone resection was avoided and the mucoperiosteal flaps completely covered the alveolar bone. Another study (Kaldahl et al., 1996a), found that sites with greater initial PPD showed greater probing depth reduction and gain of clinical attachment. Furthermore, the mean clinical attachment gain following a surgical flap procedure with osseous surgery was similar to that following root planing or a Widman flap in the deeper sites where osseous surgery was not performed (Knowles et al., 1980, Kaldahl et al., 1996a).

Residual periodontal pockets in terms of number and depth, determines the need and extent of periodontal re-treatment during the supportive periodontal maintenance period (Fardal and Linden, 2005, Ramseier et al., 2019). Thus, surgical techniques which can achieve elimination or significant reduction of the pocket depth may prevent progression of the disease and ensure the establishment of periodontal health and longevity of the teeth (Claffey and Egelberg, 1995, Matuliene et al., 2008). Furthermore, the presence of residual periodontal pockets of 6mm or more which bleed on probing, have been shown to have a higher incidence of tooth loss, compared with 4mm or less, over a period of 10 years (Matuliene et al., 2008).

Surgical periodontal therapy (with the aim to reduce or eliminate residual PPD), encompasses numerous techniques/ approaches that have been proposed by experts over numerous decades (Wang and Greenwell, 2001, Graziani et al., 2018). Historically, periodontal surgical techniques tended to involve removal of the ‘diseased’ gingiva and/or full mucoperiosteal access flaps (Kirkland, 1947, Wright, 1965) with or without osseous resection (Ochsenbein, 1958). Frequently, these techniques resulted in increased gingival recession, dentine hypersensitivity and poor aesthetic outcomes. As time progressed, along with

our understanding of healing, less invasive techniques were developed such as the Modified Widman flap (Ramfjord and Nissle, 1974), papilla preservation techniques (Takei et al., 1985, Cortellini et al., 1995, Cortellini et al., 1999) and minimally invasive techniques (Cortellini and Tonetti, 2007, Cortellini et al., 2008, Cortellini, 2012). The papilla preservation flaps were originally developed for regeneration of intrabony defects (Cortellini et al., 1995, Cortellini et al., 1999), however have also been adopted as access flaps for pocket reduction surgery also (Graziani et al., 2018), although the evidence to support their efficacy for PPD reduction is weak.

Surgical periodontal therapy techniques have demonstrated consistent success in regard to PPD reduction/ elimination and BOP in the treatment of residual pockets (Heitz-Mayfield et al., 2002). One review (Wang and Greenwell, 2001), found that in a select group of long-term studies, that mean pocket depth reduction following pocket elimination surgery was the greatest (1.77 mm), followed by Modified Widman flap (1.63 mm) and scaling and root planing (1.33 mm). This result however was at the expense of clinical attachment level, which was the greatest for pocket elimination surgery (-0.06 mm), compared with a gain in attachment for the Modified Widman flap (0.26 mm) and scaling and root planing (0.45 mm).

One systematic review (Heitz-Mayfield et al., 2002), which included seven studies, compared effectiveness of surgical and non-surgical therapy for the treatment of chronic periodontitis with a minimum follow- up of 12 months. The authors found that at 12 months following treatment, in deep pockets (PPD >6 mm), periodontal surgery resulted in greater PPD reduction (0.6mm) and CAL gain (0.2 mm) when compared with NST. In moderate pockets (4-6 mm) surgical therapy resulted in 0.4mm more PPD reduction than NST, however the latter resulted in 0.4 mm more clinical attachment level gain. Similar results have also been published more recently (Sanz-Sanchez et al., 2020), although inclusion criteria differed in regard to minimum follow-up time (6 months) and

included periodontitis cases (both chronic and aggressive). Despite differences, both NST alone and NST combined with surgical therapy were concluded as effective approaches in the treatment of chronic periodontitis (Cobb, 2002, Heitz-Mayfield and Lang, 2013, Polak et al., 2020, Sanz-Sanchez et al., 2020, Suvan et al., 2020).

Although conservative procedures have received more attention in the literature recently, there are still very few studies addressing their efficacy for the treatment of residual pockets associated with suprabony defects (Graziani et al., 2014). The simplified papilla preservation flap (SPPF) was used as a control group in two studies (Di Tullio et al 2013, Iorio-Siciliano et al 2021), which compared it with SPPF and the addition of enamel matrix derivatives. The studies found a mean PPD reduction of SPPF alone ranged from 2.2 (± 0.8) to 3.2 (± 0.6) mm, CAL gain ranged from 1.0 (± 0.6) to 1.8 (± 0.6) mm and gingival recession from 1.2 (± 0.7) to 1.4 (± 1.0) mm at 12 months following therapy. It is difficult to compare these results with the surgical studies from the 1980's and 90's, as results were presented in a different way (previously reported according to original PPD categories), however, the PPD reduction appears similar to findings in Kaldahl et al. (1996a) for the MWF group with initial PPD of 5-6mm (estimated from graph).

Heitz-Mayfield et al. (2002) also highlighted that many studies were incomplete regarding the presentation of methodology and interpretation of results in studies exploring periodontal surgery. Unfortunately, this is a common finding in the periodontal literature (Leow et al., 2016), with numerous studies omitting guidance to adhere to CONSORT guidelines. Importantly, the authors also noted that there was no data on patient reported outcomes. Although close to 20 years have passed, a more recent systemic review (Sanz-Sanchez et al., 2020) found that patient reported outcomes are still very scarce, finding that only four out of the 36 included studies presented any information on patient-based outcomes. The findings above therefore should raise significant

discussion regarding current periodontal surgical techniques based on appropriately powered clinical studies and appropriate end-points (Pihlstrom et al., 2012).

It is still not clear which (if any) surgical technique produces superior clinical, or patient reported outcomes. As our knowledge of healing and recognition of patient comfort and experience increases, there is a shift toward conservative and minimally invasive techniques (Cortellini and Tonetti, 2009) as well as adjuncts such as enamel matrix derivatives (Cortellini et al., 2008) and platelet rich plasma/fibrin (Agarwal et al., 2016, Thorat et al., 2017) . One important aspect of the healing process in periodontal surgery is revascularization of the flap, and the speed of this has been evaluated via Laser Doppler flowmetry (LDF). Two commonly used surgical flaps, the modified Widman flap (Ramfjord and Nissle, 1974) and the SPPF (Cortellini et al., 1999), were evaluated during healing using LDF (Retzepi et al., 2007a, Retzepi et al., 2007b) and found that all surgical approaches led to significant reduction of PPD at two months following. The SPPF technique however, exhibited a faster re-vascularization at four and seven days post-operatively, compared with the modified Widman flap. It is known that blood supply of the flaps at the early post-operative stages is of great importance in determining the wound healing of the operated tissues, therefore it could be argued that a more conservative flap may result in better clinical (and patient reported) outcomes.

Surgical treatment approaches aim to create a local environment which is conducive to efficient long-term maintenance for both the patient and clinician (Lindhe et al., 2008). This may be in the form of, ‘pocket elimination’, whereby the periodontal pocket probing depth reaches a level which equates to a gingival sulcus (1-3 mm in depth), or ‘pocket closure’ (PPD≤4 mm) (Lundgren et al., 2001) which is more often associated with conservative procedures.

The surgical approach to treat residual disease thus may prove more cost-effective than non-surgical maintenance in the long term (Fardal et al., 2012,

Miremadi et al., 2014), if the assumption is that future maintenance appointments would be more straight-forward and therefore requires less clinical chair-time, and the occurrence of post-therapy complications may be reduced also (Serino et al., 2001b). Furthermore, should the surgical approach prolong the life of the tooth, this would also obviate the need for expensive restorative options.

2.1.3 Need for Re-Treatment

Long term data from a number of clinical trials suggests that further breakdown (and need for re-treatment) may be greater for those treated with NST at initially deep sites (≥7 mm) when compared with ST (Kaldahl et al., 1996b, Becker et al., 2001, Sanz-Sanchez et al., 2020), however the type of surgical intervention (i.e., conservative or resective) appears to be important. Initial PPD of 4-6 mm however, shows similar long-term results (attachment/ tooth loss) between the two treatment approaches.

Pihlstrom et al. (1983) compared the outcomes of NST and ST (and subsequent regular SPC) in the treatment of moderate to advanced periodontitis (453 teeth evaluated) for 6.5 years. The authors reported that in PPD which were initially 4-6 mm, NST and ST were similarly effective in maintaining pocket reduction up to 6.5 years. For PPD ≥7 mm, the NST group experienced some recurrence of pocket depth, whilst the ST group maintained a statistically significant pocket reduction from baseline. Tooth loss over the follow-up was similar in both groups, with the NST group losing six teeth, whilst the ST group lost five teeth. No data specific data was given for the number of sites needing re-treatment for each group. Although valuable information can be taken from this long-term study, it should be noted that this study only included 17 patients initially, which had reduced to 10 patients at 6.5 years. Data were presented per tooth rather than per patient, thus does not account for clustering of progression or tooth loss in one or two patients. Furthermore, although graphs were presented,

these were difficult to decipher for specific numeric data regarding PPD reduction particularly.

Another clinical study (Ramfjord et al., 1987) compared four modalities (both surgical and non-surgical) of treatment in 90 patients with a split mouth design, with follow up of 5 years. The findings of this study were that 101 teeth (24 patients) were re-treated during the maintenance phase, of these, 44 were from the NST group, and approximately 20 from the ST groups. Two re-treated teeth needed extraction subsequently. No data was given as to the original PPD of the sites requiring re-treatment. The authors found that in the long-term, NST appeared equivalent to ST with regard to tooth loss and clinical attachment level (CAL) maintenance.

Kaldahl et al. (1996b) reported sites requiring re-treatment (CAL loss of ≥3 mm from baseline) with up to seven years of SPC following four modalities of treatment (coronal scaling, NST, modified Widman flap surgery and surgery with osseous resection) in 82 patients. The study found that the yearly incidence of breakdown sites was statistically significantly greater in the NST group compared with both surgical modalities in initial PPD≥7 mm, being 3.19% (n= 2,981 sites) for NST group, 2.09% (n= 2,967 sites) for the Modified Widman flap (MWF) surgery group and 1.36% (n= 2,494 sites) for the surgical flap with osseous resection (RPFO) group. The trend was similar for initial PPD 5-6 mm (but to a lesser extent), although the difference between the NST and MWF was not found to be statistically significant.

One study evaluating three treatment modalities (MWF, RFP and NST) in 16 participants (Becker et al., 2001) found that CAL loss of ≥2 mm at 5 years was greatest for the MWF in initial PPD ≥7 mm (n=6, 23.1%), followed by the NST group (n=3, 21.4%) and RFP0 group (n=1, 21.4%). Initial PPD of 4-6 mm demonstrated a similar pattern with regard to CAL loss with MWF having 20 sites (14.5%), NST having 21 sites (10.8%) and RFPO with 20 sites (10.4%).

A recent systematic review (Sanz-Sanchez et al., 2020) found (based on four studies) that approximately 0-14% of patients needed re-treatment following access flaps, whilst 8-29% of patients previously treated with NST. The authors also found that the weight mean incidence of CAL loss was consistently greater for NST when compared with access flaps in initially deep pockets (>6 or ≥6 mm PPD). Based on two studies (Ramfjord et al., 1987, Becker et al., 2001) weighted mean incidence (WMI) of sites with ≥2 mm CAL loss was 15.7% (95% CI 7.5 -24.0%) for NST, and 10.3% (95% CI 4.0 -16.6%) for access flaps, in initially deep pockets. A similar analysis for CAL loss ≥3 mm for different studies (Ramfjord et al., 1987, Kaldahl et al., 1996b) found that the WMI for the NST group was 3.2% (95% CI 2.6-3.8%) and 2.1% (95% CI 1.6-2.6%) for the access flap group for initially deep sites.

It should be noted also that SPC in all the studies outlined above, highlighted regular, frequent (3 -4 monthly) visits, which undoubtedly have an important role in the prevention and management of recurrence and tooth loss (Costa et al., 2015, Leow et al., 2021). It may be that the frequency and quality of the SPC appointments are a more important factor in disease recurrence/ progression than the initial mode of therapy (Becker et al., 2001, Costa et al., 2015).

2.1.4 Supportive Periodontal Care

Supportive periodontal care is a life-long phase of care, which follows the completion of the active phase of therapy (Sanz et al., 2020). SPC is thought to be essential in minimising disease progression or recurrence (Rosling et al., 2001, Matuliene et al., 2008, Trombelli et al., 2015) and therefore is an extremely important step in the long-term care of the periodontal patient.

SPC may be composed of several components which include (Leow et al., 2021):

- Interview: periodontal health symptoms, medical and social history, risk factors including tobacco use, stress and diabetes and reported plaque control regime
- Assessment: plaque and calculus deposits, periodontal health including inflammation, probing pocket depths and bleeding pockets
- Formulating: intervention needs including risk factor management, oral hygiene and retreatment
- Practical Intervention: oral hygiene coaching, instrumentation of supra- and subgingival plaque and calculus, treatment of sites with recurrence (finding of periodontitis at a previously healthy/stable site) or residual periodontitis (a deep periodontal pocket remains despite active therapy) (Graziani et al., 2018)
- Planning: interval before next SPC visit

A complex intervention, SPC requires on-going regular commitment from the patient in order to reduce risk of disease progression and subsequently prevent tooth loss (Lee et al., 2015, Ramseier et al., 2019) and maintain oral health and related quality of life (Armitage and Xenoudi, 2016).

The time between SPC visits is different for each patient, and frequency should be determined by evaluating risk factors, both systemic and local. Those with greater risk of disease recurrence or progression would require shorter intervals (e.g. 2-3 months) with those at reduced risk, having longer time intervals (Armitage and Xenoudi, 2016).

2.1.5 Outcome Measures

Research in periodontology has long been focused on clinical outcomes, including surrogate measures of health or disease such as PPD, CAL, REC, BOP and less often, tooth survival (Hujoel and DeRouen, 1995, Loos and Needleman, 2020). These outcome measures are useful in comparing interventions, however, are unable to capture the full impacts of therapies,

particularly with regard to change in symptoms, daily functioning and quality of life of the patient. Therefore, traditional research has been challenged to include outcomes which are more tangible and relevant to those most affected, the patients themselves (European Federation of Periodontology, 2013, Loos and Needleman, 2020). This might be achieved in a number of ways such as by including patients (and stakeholders) in the entire research process from study conception to publication of results, and importantly by including PROMs in the study design.

2.2 Patient Reported Outcome Measures (PROMs)

Any health status information gathered directly from a patient about a health condition or intervention without interpretation by another person, is known as a patient reported outcome (PRO) (Food and Drug Administration, 2009). Amongst others, PROs may include quality of life (QoL), health-related quality of life (HR-QoL) and oral health-related quality of life (OHRQoL) and are most often utilised to assess impacts of chronic conditions and their treatments from the patient's perspective. PROs are quite different to clinical outcomes, with main differences outlined in Table 2.

Table 2. Patient reported outcomes versus clinical outcomes.

	Patient reported outcomes	**Clinical outcomes**
	Subjective measure of disease or health status (e.g., quality of life, patient experience) as reported by the patient.	Objective measure of disease or health status (e.g., tooth loss, mortality) as assessed by a healthcare professional.
Aim(s)	Evaluate impact of a disease and/or treatment from the	Measure disease status, progression, efficacy of

	Patient reported outcomes	**Clinical outcomes**
	patient's perspective.	treatment and safety.
Value	• Guides patient-centred care • Guides shared decision-making • Informs on cost-benefit of treatments • Encourages patient engagement and motivation • Measures psycho-social elements of disease status and interventions	• Guides clinical decision-making • Informs on cost-benefit of treatments, regulatory approvals • Objective
Limitations	• Subject to recall bias • May not reflect severity of disease status or objective measures of treatment efficacy • May be influenced by patient background or culture • Instruments used to measure may have limited scope in assessment of multiple domains	• May be susceptible to clinician bias or measurement error • Doesn't capture patient experience • Often doesn't align with patient priorities (e.g., aesthetics, every day activities)

Measurement of PROs through a variety of tools (i.e., PROMs) have become a crucial element of clinical research and benefits of including PROMs include (Williams et al., 2016);

- Impact of a disease and/or treatment is best judged by the patient – particularly with regard to pain, function, symptoms and quality of life
- PROMs are essential for patient-centred care and can be an aid to shared decision-making in the clinical setting.
- Have the potential to improve quality and safety of healthcare by informing on the effectiveness of treatment and negative (or positive) outcomes/ events

Globally, PROMs are still not embedded in national health systems or national registries (Williams et al., 2016), which limits the information gained that could have a significant impact on country specific national guidelines for the management of a particular condition. On a positive note, there is evidence that some countries such as the United Kingdom, the Netherlands, Sweden and the United States, are working to implement the routine application of PROMs in selected areas of Medicine on a national scale (Williams et al., 2016). The growing number of studies with emphasis on PROMs as a primary or secondary outcome has also led to an extension to the CONSORT reporting guidelines (Moher et al., 2010) specifically for reporting patient reported outcomes (CONSORT PRO) (Calvert et al., 2013) and guidelines for conducting methodological studies based on PROMs (Gagnier et al., 2021) established. Importantly, research funders have greater awareness of its importance (Snyder et al., 2021). Furthermore, the development of focussed communities such as the PROTEUS (Patient-Reported Outcomes Tools, Engaging Users and Stakeholders) consortium were developed in order to promote high standards of PRO methods in both clinical trials and clinical practice, ultimately for patient benefit (The PROTEUS Consortium, 2022).

The United Kingdom has made considerable efforts to integrate PROMs in medical routine clinical practice within the National Health Service (NHS) England by launching the National Patient Reported Outcome Measures

Programme since 2009 (https://digital.nhs.uk/data-and-information/data-tools-and-services/data-services/patient-reported-outcome-measures-proms).
Following this, in 2014, the UK Competitions and Market Authority (CMA) mandated collection of PROMs from independent (privately funded) health-care facilities also (Competition and Markets Authority, 2014). The same level of implementation has not occurred in Dentistry however, with most PROMs investigations led by researchers or individual NHS Trusts.

2.3 Features of PROMs

PROMs can be categorised into either generic or condition/disease-specific. When considering HRQoL, generic tools can be used for any disease or condition (including oral), and therefore allow comparisons to be made, however, these tools tend to lack sensitivity (Churruca et al., 2021, Kontodimopoulos et al., 2022) particularly when discriminating between degrees of morbidity (Brennan and Spencer, 2005, Bharmal and Thomas III, 2006). Additionally, generic instruments attempt to capture a broad range of experiences (e.g., self-care, physical, emotional and social aspects), may be short and are often ideal to use for large scale populations. In contrast, condition-specific PROMs have a greater ability to detect change over time (responsiveness) in a patient's particular condition therefore are more appropriate for specific populations where treatment outcomes are a focus (Grande et al., 2009).

The development and use of appropriate PROMs for a given situation is crucial to maximise the amount of accurate information gathered. Therefore, the content (items) of a questionnaire are most commonly derived from in -depth interviews of those likely to ultimately complete it, along with other sources (i.e. literature reviews or clinical opinion) (Locker and Allen, 2007). Subsequently, questionnaires are evaluated for important features such as 'reliability', 'validity' and, 'responsiveness' in a variety of populations.

2.3.1 Reliability, Validity, Responsiveness and Minimally Important Difference

Psychometric strength of a PROM is important to capture the impact of a disease or treatment. Reliability and validity are two psychometric properties which are essential to any instrument, and both are routinely evaluated in order to support use and results of particular tools (Frost et al., 2007, Gagnier et al., 2021) .

In the research environment, reliability refers to the ability to reproduce a measure/ outcome when repeated randomly in the same stable subject or population (Johnston et al., 2022). Additionally, for PROMs, the instrument should be able to distinguish between individuals. Reliability is calculated statistically. There are two main attributes of reliability, consistency i) across time (test-retest reliability) and ii) across items in the tool (internal consistency reliability). Multi-item scales are most often estimated by internal consistency reliability, and this relates different items in the tool to each other (Frost et al., 2007). Internal consistency is usually indexed by Cronbach's coefficient alpha which represents a ratio of between person variance and total variance (between people and responses to different items). An appropriate interval for test-retest reliability is usually determined to not be so short that memory plays a key role, nor too long that changes have occurred in the construct over time. Most often reliability coefficients are in the range of 0 and 1, with a threshold of 0.7 representing adequate reliability (Frost et al., 2007). A lack of reliability in a given tool can lead to complication, as this can mask true intervention effects due to random error (Johnston et al., 2022).

Validity describes whether a tool is measuring what it is intended to measure and not something else. In general, constructs in an instrument which are related should have strong correlation, whilst the opposite is true for distinctly different constructs. Three subtypes of validity that are most commonly described include; i) content validity, ii) criterion validity and iii) construct validity

(Frost et al., 2007, Johnston et al., 2022). Content validity is the 'relevance and comprehensiveness of the content contained in the measures' (Johnston et al., 2022), that is, it is the degree to which a tool measures the relevant and important aspects of constructs that it was developed to assess. Criterion validity is the extent to which a measure agrees with an accepted external standard measure and is usually not applicable for PROMs (as there is typically no standard). Construct validity is the extent to which a measure performs with regard to seemingly sensible or logical relationships between assessment constructs/items. For example, we might expect that patients with numerous mobile or missing teeth will generally have more difficulty chewing than those who don't.

Responsiveness is a tool's ability to detect change over time. This aspect of a tool becomes particularly important when evaluating longitudinally (e.g., interventional trials), for example, whereby administration of the tool is often before and after particular interventions. Thus, it is important that a chosen tool can distinguish between patients that have had a positive, negative or lack of impact (Revicki et al., 2008) over time. Evaluating responsiveness of an instrument is usually conducted by comparing change in scores in those, who by other criteria have improved, deteriorated or stayed the same.

Minimally important difference (MID) refers to the smallest score or change in score that would likely be deemed important or meaningful from the patient's perspective (Guyatt et al., 1987, Jaeschke et al., 1989, Guyatt et al., 2002, Revicki et al., 2008). MID adds extra information for clinicians and policy-makers (beyond statistically significant differences between groups), to help interpret if the effect of an intervention has clinical relevance (Troosters, 2011). The emphasis to include MID in clinical trials with PROMs has also led to recommendation(s) for inclusion in systematic reviews (Prinsen et al., 2018, Schünemann et al., 2022), however in periodontology, few studies report this (Graziani and Tsakos, 2020).

2.4 Oral Health-Related Quality of Life in Periodontology

2.4.1 Oral health-related quality of life (OHRQoL) and Periodontitis

Moderate-certainty evidence suggests that patients with periodontitis have worse OHRQoL when compared with healthy/ stabilised patients (Acharya et al., 2009, Araujo et al., 2010, Bernabe and Marcenes, 2010). Most frequently, patients with periodontitis report negative impacts in the functional (i.e., eating), psychological status and well-being (i.e., self-confidence, socialising) and pain domains (Shanbhag et al., 2012, Botelho et al., 2020). It should also be highlighted that commonly, periodontitis presents in people with other chronic systemic conditions such as cardiovascular disease, DM, obesity and chronic kidney disease (Linden et al., 2013). When a single individual presents with multiple medical conditions (two or more), this is termed, 'multimorbidity' (World Health Organization, 2016b) and most high income countries consider this the norm rather than the exception (Academy of Medical Sciences, 2018). The evidence on multimorbidity with regard to prevalence, effective treatments and impact on quality of life is fragmented, and as such, has been proposed as a research priority going forward (Academy of Medical Sciences, 2018). It is therefore not surprising that there is a lack of evidence informing on the treatment of periodontitis on patients with diabetes with regard to PROMs.

2.4.2 OHRQoL and Periodontal Therapy

Non-Surgical Therapy

There is currently a weak but consistent evidence-base to support a positive impact on OHRQoL in the treatment of periodontitis following non-surgical therapy. In recent years, a number of systematic reviews have been published (Shanbhag et al., 2012, Baiju et al., 2017, Botelho et al., 2020, Khan et al.,

2021, Wong et al., 2021), all of which concluded a beneficial effect of NST on OHRQoL.

Wong et al. (2021), published an 'umbrella review' of systematic reviews on the topic, which included three systematic reviews addressing the effect of periodontal therapy on HR-QoL and OHRQoL (Shanbhag et al., 2012, Baiju et al., 2017, Botelho et al., 2020). One of the included systematic reviews was deemed as of 'critically low quality' (Baiju et al., 2017), whilst the remaining two were of 'moderate' quality according to the AMSTAR2 checklist. The main factors leading to these quality assessments were a lack of appropriate assessment/ discussion of risk of bias of included studies, lack of explanation for heterogeneity between studies and no information on sources of funding. Despite this, when bringing the three systematic reviews together, the majority of studies reported an improvement in OHRQoL following NST. The authors also highlighted that no systematic reviews reporting on NST and HR-QoL existed, which is a reflection of the lack of research focussed on NST and general QoL.

Shanbhag et al. (2012) found that nine out of 11 included studies reported a statistically significant improvement in OHRQoL after NST. The included studies were a combination of prospective case series (n=7), a controlled before-after study (n=1) and RCTs (n=3). Quality assessment using the Newcastle-Ottawa scale, found that all studies were of 'medium' methodological quality due to a variety of reasons including lack of reporting on intra/inter operator calibration, sample size/power calculation and high drop-out rates. There was a lack of agreement on the effect size, which was reported in four studies, and ranged from 0.27 to 0.8, however different time points were chosen for administering the follow-up questionnaires (3 – 9 weeks), which may be important. One study (Ohrn and Jonsson, 2012) found no statistically significant improvement in OHRQoL following NST possibly owing to a small sample size (n=42) and subsequent lack of power, and/or a longer follow-up

period (3 months). A second study (Bajwa et al., 2007) also did not find a statistically significant difference after NST using the OHIP-14 questionnaire 6 months later. The reasons for this may have been due to the large drop-out rate (57%, n=73), therefore, a responder bias was possible (i.e., those that responded could have had less severe disease, be more health conscious, more compliant) than those that dropped out. Additionally, the study was set in a hospital environment and no time limit was set for the NST period. The authors reported that NST could have spanned 6 months to 1 year, which may be considered significantly longer than other studies which were included in the systematic review. Furthermore, Shanbhag and co-workers were unable to carry out a meta-analysis, principally due to heterogeneity of both clinical and methodological study conduct, but also because of differing definitions of periodontitis, OHRQoL measures used and duration of follow-up. Currently, it is not clear whether a longer follow up period affects the OHRQoL (i.e., Does the magnitude of effect diminish over time?) and clearly, the frequency and nature of maintenance visits during that period may also affect OHRQoL.

In agreement with the findings of Shanbhag et al. (2012), one systematic review (Botelho et al., 2020) additionally conducted a meta-analysis (based on seven cohort studies). In contrast to Shanbhag et al. (2012), this systematic review had less stringent inclusion criteria (e.g., included patients with co-morbidities), and studies which were published following the previous review (eight studies published subsequent to 2012). The authors conducted the meta-analysis on studies with similar methodologies, that used the OHIP-14 questionnaire and conducted subgroup analyses according to follow-up time. The follow-up times of 1-2 weeks (three studies), 3-4 weeks (two studies) and 6-12 weeks (three studies), included different studies for each period. A beneficial effect on OHRQoL following NST was found, and a mean difference of 2.49 ($p<0.01$) 1-2 weeks (based on three studies, 93 participants), and 8.94 ($p<0.01$) 3-4 weeks (based on two studies, 175 participants) following NST was calculated. 6-12 weeks after NST, the mean difference was found to be 6.49 ($p<0.01$) (based on

three studies, 251 participants). A recent systematic review (Khan et al., 2021) corroborates the findings of both previous systematic reviews with regard to positive impact of NST on OHRQoL.

Most studies assessing OHRQoL and NST are prospective case series/ cohort studies with generally small numbers of participants (most often n < 65) with a lack of control group and a variety of follow-up periods (range 1-12 weeks) (Shanbhag et al., 2012). Due to this heterogeneity, it's difficult to directly compare studies with regard to effect sizes, although the overwhelming majority do report statistically significant improvements in OHRQoL.

Saito et al. (2010) conducted a prospective cohort study at Tokyo Dental College and Keio University Hospital and included 58 participants with periodontitis. OHRQoL (using a Japanese version the oral health-related quality of life model for dental hygiene) was determined at baseline and 3-4 weeks after therapy. A significant number of participants dropped out between BL and post therapy (n=39, 40%) and no explanation was provided for this, which has implications for attrition bias. The authors reported a statistically significant improvement in OHRQoL following NST in 76% of participants and classed the mean effect size as moderate (0.51).

One hospital-based study which included 183 participants (Nagarajan and Chandra, 2012), found that 6 months after therapy OHRQoL improved in most participants (using the OHQoL-UK questionnaire). This study however was judged as having a medium risk of bias and lacked information on the exact procedures carried out (i.e., some participants received only NST, whilst some received a combination of both NST and ST). The relative contribution of ST to the overall outcome was therefore unclear.

Brauchle et al. (2013) conducted a case series with 82 periodontitis patients and 11 controls, using the German OHIP-14 questionnaire median OHIP-14 scores significantly reduced from baseline (6.3) to 6-8 weeks following NST

(4.8, p<0.001), representing an improvement in OHRQoL. The authors found those patients with the most severe disease (PPD>7mm) had the greatest improvement in OHRQoL, which may be an indicator that patients with the greater severity of disease appear to benefit the most, however researchers should also be aware of the, 'floor effect' (lower scores are more difficult to reduce by the same magnitude as higher scores) (Bajwa et al., 2007)

Only a few RCTs exist (Ozcelik et al., 2007, Aslund et al., 2008, Tsakos et al., 2010, Jonsson and Ohrn, 2014), and in all studies, OHRQoL was a secondary outcome, thus due to small sample sizes (range: 45-60 participants), these studies lacked the power to draw firm conclusions from the results (all four studies reported an improvement in OHRQoL following NST). When comparing these studies, the follow-up questionnaire was administered at significantly different times, from one week (Ozcelik et al., 2007) to 12 months (Jonsson and Ohrn, 2014), but despite this, Tsakos et al. (2010) (follow-up of 4 weeks) and Jonsson and Ohrn (2014) (12 months follow-up) shared similar findings with regard to the smallest change in the PROM score that a patient would deem important (minimally important difference), indicating that the benefits of NST could have lasting effects beyond 12 months. Tsakos et al. (2010) found the MID for CS-OIDP varied between 5.3 to 5.7 with a small to moderate effect size of 0.44, whilst Jonsson and Ohrn (2014) found for the OHQoL-UK questionnaire, a MID of 5.1 with a small effect size of 0.3.

In summary, NST in the treatment of periodontitis, is consistently associated with statistically significant improvements in OHRQoL as demonstrated in a large number of clinical studies. This positive impact on OHRQoL appears to be consistent despite varying follow-up periods with varying effect sizes (range from 0.27-0.8) and MIDs (5.0-5.7). Larger, high quality clinical studies (ideally with PROMs as a primary outcome) are required in order to confirm these findings and importantly, to more accurately determine the minimally important difference and effect size.

Surgical Therapy

As demonstrated with NST, PROMs have become increasingly important to determine the impact(s) of therapeutic interventions on patients. In contrast to NST, ST however has received less attention in periodontal research with regard to PROMs.

Shanbhag et al. (2012) found that only three studies (Ozcelik et al., 2007, Saito et al., 2011, Nagarajan and Chandra, 2012) included PROMs in the evaluation of surgical therapy, and with typically short follow-up periods (one week to six months). Additionally, risk of bias was judged to be 'medium' between the studies with the main issues being that generalisability of the results and sample size/ power calculation were generally not discussed. Surprisingly, the evidence on the impact of ST in the treatment of periodontitis on OHRQoL is still scarce and inconsistent between studies (Baiju et al., 2017).

One of the earliest studies to report on PROMs and surgical therapy (Lee et al., 2002), reported on 33 private practice patients with chronic periodontitis in Korea. All patients underwent a modified Widman flap surgery in more than 4 areas of the mouth, as well as osteoplasty (if required). The patient reported outcome questionnaire was composed of 16 items with a four-point Likert response format and mainly explored areas of patient expectation and satisfaction. Patient dissatisfaction was mainly related to a lack of information on aetiology, progress, prognosis and preventative methods from the dental team. The results of this study found that patient satisfaction significantly decreased 3 months after treatment compared with baseline. Although the results are interesting, we must interpret these with caution as there are a number of weaknesses such as lack of information on sample size calculation, description of procedures and how the questions in the questionnaire were chosen, nor if this was a validated questionnaire.

Another study (Ozcelik et al., 2007), was one of the first randomised controlled trials to include PROMs in their outcomes. This study, which included 60 participants, used the General Oral Health Assessment Index (GOHAI) and the oral health impact profile (OHIP-14) questionnaire to assess participants every day for one week, after NST, surgical therapy (ST) or surgical therapy with enamel matrix derivatives (STE). Statistically significant differences between groups were noted from the first post-operative day, whereby the ST group experienced worse OHRQoL when compared with the NST and STE groups. The ST group experienced greater functional limitations, more pain and discomfort, and more psychological and behavioural impacts than the other groups, and the NST and STE were similar. The authors concluded however, that all groups experienced an improvement of OHRQoL between baseline and 7 days post-operative. The study had a small sample size, and it was unclear how this was determined, therefore other differences between groups may not have been detected due to insufficient numbers. Additionally, the follow-up time is extremely short, so we are unable to determine if this difference in OHRQoL is sustained beyond one week post-operatively.

Nagarajan and Chandra (2012) evaluated a cohort of 191 chronic periodontitis patients following NST therapy and in some 'high' risk patients, surgical therapy, 6 months following treatment. The patients were administered the oral health quality of life, UK (OHQoL-UK) questionnaire (McGrath and Bedi, 2001) at baseline and 6 months. The authors found a statistically significant improvement in OHQoL-UK scores before and after surgical therapy (-10.95, p=0.001). Once again, this study did not report on how the sample size was determined, factors associated with, 'high' risk patients (i.e., how they were selected) nor any detail on the surgical technique or operators, so results must be interpreted with caution. Additionally, no estimation of effect size was given.

One research group from Japan (Saito et al., 2011, Makino-Oi et al., 2016) reported on PROMs after both NST and surgical therapy firstly in a small pilot

study of 21 participants (Saito et al., 2011) and subsequently, in a multi-centre trial of 76 participants (Makino-Oi et al., 2016). Saito et al. (2011) recruited 45 participants with moderate to severe periodontitis and evaluated OHRQoL using the Japanese version of the oral health-related quality of life questionnaire (Sato et al., 2007) with seven domains. The participants completed a baseline questionnaire (phase I), NST was carried out (n=42) and a minimum of 3 weeks of healing was allowed prior to the next questionnaire (phase II, n=21) and finally, a portion of the patients (n=16) that required further treatment, underwent open flap debridement with 12-14 weeks healing before the final questionnaire (phase III). The results showed a statistically significant improvement in OHRQoL scores between phases I and II (8.9, $p<0.01$, effect size 0.8) and phases I and III (10.6, $p<0.01$, effect size 0.9) however this was not significant between phases II and III (1.7, $P>0.05$, effect size 0.2). The seemingly small change in OHRQoL score following ST (after NST) might indicate that the majority of tangible benefit for the patient occurs following NST, whilst ST may add little benefit from the patient's perspective. The OHRQoL score following surgical therapy was negatively corelated with the percentage of sites PPD≥4 mm (i.e., a greater improvement in proportion of sites ≥4 mm correlated with a better OHRQoL score). Seven out of 16 patients experienced an increase in OHRQoL score (worsened QoL) after surgery, despite having a better QoL after NST. The main concerns following ST for these patients were, 'eating and chewing,' and 'psychological function', similar to those after NST (Saito et al., 2010) (Saito et al., 2010) but the authors also highlighted the fact that OHRQoL fluctuates in different phases in every patient.

Makino-Oi et al. (2016) recently published results of a three-centre prospective clinical trial which included 76 participants with moderate to severe periodontitis, with a similar study design to that of Saito et al. (2011) in regard to phases. The difference in this study was that following phase II, 26 participants underwent further NST to address residual pockets (NST-2) whilst 50 participants had surgery (phase III). Both the NST-2 and ST groups were re-assessed 12-14

weeks later. A statistically significant difference was found for both the NST-2 group and surgical group from baseline (phase I to III), but the extent of improvement was more pronounced for the surgery group ($p<0.001$) when compared with the NST-2 group ($p<0.05$). The findings of this study echoed that which was found in the related pilot study (Saito et al., 2011), that no statistically significant difference could be detected in OHRQoL score between phase II and III.

The findings from both these studies appear to highlight that our patients may not report further improvements in regard to OHRQoL domains after surgical therapy from that achieved by non-surgical therapy. This may be because the greatest tangible change for the patient occurs following NST. Alternatively, the PROM tools used may not be sensitive enough to detect a change between time points (lack of responsiveness).

A search for studies has not identified any which have compared conservative surgical techniques with resective periodontal flaps (with osseous resection) or NST with PROMs in the treatment of residual/ recurrent disease. Whilst conservative surgical techniques may offer benefits in regard to healing (i.e., reduced pain, sensitivity), it is important to know if this translates to an impact on our patients' everyday life and should be a research priority going forward, considering the increasing popularity of these techniques.

In summary, multiple treatment approaches (both non-surgical and surgical) can be employed which will lead to a successful clinical outcome. There has been a clear shift toward conservative and minimally invasive surgical techniques (for regenerative procedures) in the last two decades to improve the healing process and pain related to post-surgical complications such as swelling, wound dehiscence or haematomas and reduced clinical chair time (Tonetti et al., 2004, Cortellini and Tonetti, 2009). However, the evidence that conservative flaps, such as the SPPF, is effective in the treatment of residual disease is weak, when compared with more invasive flaps (e.g., access flap with osseous

resection). Importantly, very few studies have assessed the impact of periodontal surgery on oral health-related quality of life and general quality of life.

OHRQoL following treatment of periodontitis in patient with co-morbidities.

One recently commissioned systematic review (European Federation of Periodontology) on the effect of treatment of stage IV periodontitis on systemic health (Orlandi et al., 2022) found that quality of life was rarely reported in the studies. The authors therefore identified the need for future RCTs to clarify the impacts of periodontal treatment on patients with co-morbidities. Additionally, a recently updated Cochrane systematic review (Simpson et al., 2022) found that from the 35 included studies, only three studies reported on HRQoL (D'Aiuto et al., 2004, Mizuno et al., 2017, Vergnes et al., 2018). Different QoL tools and time points were utilised amongst the studies, so although difficult to compare, the authors reported that there was limited evidence of a possible benefit in QoL in individuals with diabetes following periodontal therapeutic intervention (Simpson et al., 2022).

2.4.3 OHRQoL and Long Term Supportive Periodontal Care

Currently no prospective studies exist evaluating OHRQoL in periodontitis patients in long-term SPC. This may not seem surprising, considering the significant time and costs involved in running a trial such as this, however, the insight into impacts during SPC would be invaluable. One secondary analysis of PROMs (Mendez et al., 2021) from a previously conducted RCT (Angst et al., 2019) which compared oral hygiene instructions and oral prophylaxis (test) with subgingival instrumentation (control) in 62 participants, every 3 months over 24 months of follow up reported no statistically significant change from BL to 24 months. The authors cited a low initial OHIP-14 of the participants upon entering the study as a reason for minimal change, and the fact that in SPC

endpoints of therapy are often not achieved (as might be the case with active periodontal therapy). A MID estimation of 4.1 was found for this group of patients using the distributed-based approach, and 33.9% of respondents achieved the MID or above.

2.5 Commonly used PROMs in Periodontology

A number of PROMs have been used in the context of evaluating periodontitis and interventions in periodontal research. No consensus currently exists as to the best tool (or combination) to use. Presently, three PROMs tend to dominate the periodontal literature (Oral Impacts on Daily Performance, Oral Health Impact Profile-14 and Geriatric Oral Health Assessment Index) possibly due to familiarity to particular research groups, ease of use and/or ease of comparison with other studies.

2.5.1 Oral Impacts on Daily Performance (OIDP)

Originally developed as a modification of the World Health Organization's International Classification of Impairments, Disabilities and Handicaps (World Health Organization, 1980), the OIDP questionnaire was adapted for dentistry by Locker (Locker, 1988). Primarily, Locker introduced different levels of outcome variables (Figure 1) corresponding to oral status/ oral impairments (level 1), early negative impacts resulting from oral health status i.e., pain, discomfort, aesthetics (level 2) and ability to perform daily activities i.e., physical, social and psychological (level 3) (Adulyanon and Sheiham, 1997), with the main emphasis being on level 3.

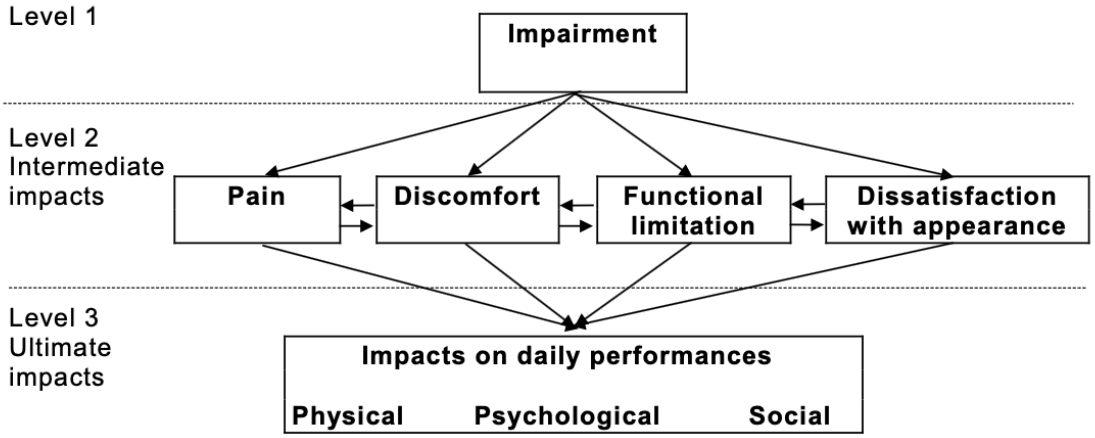

Figure 1. Framework from which OIDP questionnaire was developed [(image taken from Adulyanon and Sheiham (1997)]

The OIDP questionnaire was originally designed to assess eight daily performances (Adulyanon and Sheiham, 1997) which included;

- Eating and enjoying food
- Speaking and pronouncing clearly
- Cleaning teeth
- Sleeping and relaxing
- Smiling, laughing and showing teeth without embarrassment
- Maintenance of usual emotional state
- Carrying out major work or social role
- Enjoying contact with people

The questionnaire quantifies the impact of each performance by evaluating both frequency and severity over a set time period (e.g., past 3 or 6 months) on a scale from 0 to 5 where 0 is 'never' affected and 5 is 'frequently' affected (nearly every day). Similarly, severity is scored from 0 to 5, with 0 representing 'none' and 5 is 'very severe'. The total impact score is then calculated, which is all

performance scores (frequency multiplied by severity) added together, then divided by the maximum possible score and multiplied by 100 (to give a percentage score). A modified version proposed by Tsakos et al. (2001) separated sleeping and relaxing into two distinct performances and added an additional item (light physical activities).

The original OIDP was shown to have satisfactory construct and criterion validity (Adulyanon and Sheiham, 1997) and reliability (Kappa for frequency scoring = 0.95-1.0, Kappa for severity scoring – 0.57-1.0). Internal consistency using Cronbach's alpha was 0.67. Subsequently, the modified version of the questionnaire (Tsakos et al., 2001) was confirmed to be valid (with regard to reliability and validity) when assessed with both a Greek and British population. Interestingly, the authors found the addition of the two performances did not significantly affect the overall OIDP score, as their prevalence was very low. Additionally, psychometric properties of the OIDP questionnaire have been successfully tested in multiple adult populations in countries including Norway, Tanzania, Thailand, United Kingdom and Greece (Adulyanon et al., 1996, Tsakos et al., 2001, Masalu and Åstrøm, 2003, Åstrøm et al., 2005).

A major advantage of the OIDP questionnaire is the ability to ascertain the patient's view on the cause of an impact (e.g., tooth mobility), attributing them to a variety of conditions. When a performance is affected, the questionnaire delves further and asks the condition which caused the symptom. A condition-specific score thus can be generated (only counting the performances affected by a particular condition) in addition to the generic score (all performances included). The clear advantage of the condition-specific OIDP (CS-OIDP) score is obtaining a snapshot of the impact of certain diseases and their relation to outcomes. Furthermore CS-OIDP could give policy-makers and healthcare planners clearer insight as to the likely treatment needed related to an impact.

2.5.2 Oral Health Impact Profile

The Oral Health Impact Profile (OHIP) questionnaire was developed originally by Slade and Spencer (1994) and is a 49-item questionnaire which evaluates seven domains (Allen, 2003):

- Functional limitation
- Pain
- Psychological discomfort
- Physical disability
- Psychological disability
- Social disability
- Handicap

Similar to the OIDP questionnaire, responses are via a Likert scale from 0 to 4 (0 = never and 4 = very often). Frequency impacts are calculated by adding all negative impacts (3 or 4 according to the response scale) for the 49 statements. Severity/ relative importance of the seven impacts is calculated by a weight as a result of using 'Thurstone's paired comparison' technique (Slade and Spencer, 1994, Allen, 2003). An overall score can then be calculated according to the 49 items. Once again, the OHIP was found to have satisfactory construct and criterion validity, and addition to reliability (Slade and Spencer, 1994).

Acknowledging the lengthiness of this questionnaire, Slade and co-workers modified the questionnaire (Slade, 1997) and developed a short-form of the OHIP, with a subset of 14-items (OHIP-14). This subset of 14-tems still covered the 7 domains from the original questionnaire and was found to have high reliability and validity (Slade, 1997). OHIP-14 has been widely used in the evaluation of periodontitis (and treatments), as demonstrated by a number of recent systematic reviews (Shanbhag et al., 2012, Baiju et al., 2017, Khan et al., 2021, Wong et al., 2021).

2.5.3 Geriatric Oral Health Assessment Index

The Geriatric/General Oral Health Assessment Index (GOHAI) was initially developed with the intention of evaluating the impact of oral diseases in older populations (Atchison and Dolan, 1990). The tool consists of 12-items which are reported to cover three underlying themes/ constructs (physical function, psychological function and pain and discomfort) over the past 3 months (Graziani and Tsakos, 2020). An example of the 12 statements in the GOHAI is, 'how often did you feel uncomfortable eating in front of people because of problems with your teeth or dentures?' with the options to respond being a 6-point Likert scale from 0 to 5 (0 – never, 5 = always). Responses to each of the 12 statements are added together, giving an overall score from 0-60.

The GOHAI is commonly used to evaluate the impacts of periodontitis in adult populations and has demonstrated adequate validity and reliability (Atchison and Dolan, 1990, Ozcelik et al., 2007).

2.5.4 Oral Health-Related Quality of Life - UK

The UK oral health-related quality of life measure (OHQoL-UK) was developed by McGrath and co-workers (McGrath and Bedi, 2001, McGrath and Bedi, 2002) to specifically evaluate perceptions of how oral health affects life quality in the United Kingdom. The PROM consists of 16 questions which evaluates both 'effect' and 'impact' of oral disease on oral health-related quality of life and was also designed to show both negative and positive effects.

2.5.5 Global self-ratings of oral health

Global self-ratings of oral health (GSROH) were initially utilised as a validating tool for multiple item instruments, such as the OIDP or OHQoL-UK (Locker, 1997), however since then, has been utilised a simple, time and cost-effective way to assess patient perceptions in large population studies (Thomson et al., 2012). The reason for this, is that most often GSROH are single-item questions

which are straightforward and quick to answer and are a useful summary of how individuals rate their own oral or general health.

As with any PROM, GSROH are subjective and it is unclear which frames of reference individuals use for these single-item questions (e.g., physical or mental state and/or the presence or absence of disease) (Locker et al., 2005). They have been advocated for use as an 'anchor' in calculating minimally important difference (Revicki et al., 2008) and this has been carried out for certain tools such as the OIDP (Tsakos et al., 2010).

2.5.6 General quality of life measures

General health-related quality of life (HR-QoL) measures are seldom utilised in dentistry. A number of reasons for this lack of engagement may exist, one of which includes that HR-QoL instruments may be perceived as too generic, thus lacking sensitivity to capture the impact of oral diseases. HR-QoL tools more commonly used are the Short-Form Survey (SF-36) and the EuroQol (EQ-5D) tools and have advantages over OHRQoL tools, as their results can be converted into numerical values and used for economic evaluation.

The EQ-5D questionnaire (EuroQol Group, 1990) is a non disease-specific questionnaire which sought to describe and value health states. The questionnaire was originally designed to be used in large scale community or population-based surveys as a self-administered tool, therefore was purposely made short, to not burden subjects participating in studies. The EQ-5D evaluates five dimensions of health:

- Mobility
- Self care
- Usual activities
- Pain and discomfort
- Anxiety and depression

A patient evaluates each of the dimensions of health according to 3 levels (EQ-5D-3L) or 5 levels (EQ-5D-5L) of impact/ intensity. Additionally, a patient's health state that day is also ascertained by means of a visual analogue scale. A description of the person's health state is then gained (represented by five numbers e.g., 11231) which can then be converted to a single number (index value) which can help inform on healthcare decisions. The EQ-5D is translated into over 200 languages and has been evaluated in a variety of populations and age groups (EuroQuol Group, 2022). Further detail on attributing health states and interpreting the single index value is given in Chapter 4.

Although OHRQoL instruments are increasingly used in periodontal research, generic QoL instruments are rarely, if ever, used either as a standalone PROM or in combination with an OHRQoL instrument. The additional information gathered from using a generic QoL instrument could provide valuable insight into how OHRQoL and QoL might be related in the context of periodontal treatments and provide further information on more general dimensions of health.

2.6 Incorporating PROMs in healthcare

Although the importance of PROMs is gaining attention within research, this is not commonly reflected in their adoption by organisations delivering healthcare. Organisations may face challenges when attempting to implement PROMs, which include choosing the most appropriate PROM, training of those involved with delivering the PROM (if required), developing reporting systems and interpreting and implementing relevant findings (Foster et al., 2018).

One recent systematic review (Foster et al., 2018) evaluated the barriers and facilitators to implementing PROMs by evaluating already published reviews (not restricted to just systematic reviews) and included six studies. The settings included in the reviews ranged from 'any healthcare setting' to palliative and cancer care. The authors divided the results into five stages of implementation,

namely; Purpose, Designing, Preparing, Commencing, and Reflecting and Developing.

Key findings are listed below:

1) Purpose
    - Aligning PROMs with external policies (e.g., clinical practice guidelines) facilitated use as clinicians saw them as part of routine professional practice
    - When used for an individual patient (for patient-centred care), then PROMs were facilitated
    - If the aim was to monitor clinical performance, this served as a barrier to implementation
2) Designing
    - Choice of PROM was important. If clinicians thought that the PROM was valid, relevant, useful and user friendly, this facilitated implementation
    - Support for patients completing the PROMs and format (e.g., electronic administration was favoured) facilitated implementation due to a decreased burden on clinical and administrative staff
    - Concise and easy to understand reporting systems (e.g., graphs) that assist to utilise PROMs data in work facilitated implementation
    - Planning and involving all clinicians and administrative staff in the implementation discussions facilitated implementation
3) Preparing
    - Spending time to engage and educate clinicians on the value of PROMs was a clear facilitator to successful implementation

4) Commencing
    - Barriers to implementing PROMs arose when the 'burden' of PROMs fell on a small proportion of clinicians and when adapting to individual patients. Flexibility for clinicians to adapt the PROM was important to implementation.
5) Reflecting and Developing
    - Very little data, however when staff were able to give constructive feedback which was subsequently used to improve the process, this was a facilitator for implementation.

Dentistry is possibly even slower than Medicine to implement PROMs in research and routine practice (Porter et al., 2016, Stover et al., 2021, Singhal et al., 2022). In Periodontology, the call for action to include PROMs in clinical studies was seen over 20 years ago (Heitz-Mayfield et al., 2002, Lindhe and Palmer, 2002) and recently the message has been re-enforced in the publication of the European clinical guidelines (Sanz et al., 2020, Herrera et al., 2022), yet the adoption of PROMs in research is still not routine.

Therefore, periodontitis detrimentally affects OHRQoL, however therapeutic interventions (by way of NST) appear to improve this. It is unclear whether ST improves OHRQoL substantially when evaluated independently to NST nor if patients with co-morbidities afford the same benefits in OHRQoL following therapeutic interventions for periodontitis. However, evidence in Medicine suggests that co-morbidities negatively affect QoL changes when receiving treatment for cancer (Cummings et al., 2018, Arneja and Brooks, 2021). Presently, we have no knowledge on whether NST and/or ST affects general HR-QoL and if there is a relationship between OHRQoL, QoL or clinical outcomes following treatments. Finally, little information on SPC with regard to benefits/harms and patient-based outcomes exists.

3. STUDY HYPOTHESES AND RESEARCH QUESTIONS

A review of the literature was presented in Chapter 2, and through this, gaps in the existing knowledge were identified to inform on the impact of a variety of treatment modalities in the treatment of periodontitis on OHRQoL and QoL and medically compromised patients. Additionally, the lack of information available regarding periodontitis patients in SPC was identified. This has led to the development of the following study hypotheses and related research questions;

Study hypothesis 1: Non-surgical periodontal therapy (NST) in the treatment of stage III/IV periodontitis is associated with an improvement in OHRQoL and QoL.

Research question 1: What is the impact of NST on both OHRQoL and QoL?

Research question 2: What is the relationship between OHRQoL and QoL following NST?

Study hypothesis 2: Surgical periodontal therapy (ST) in the treatment of stage III/IV periodontitis is associated with an improvement in OHRQoL and QoL.

Research question 3: What Is the impact of ST on both OHRQoL and QoL?

Research question 4: What is the relationship between OHRQoL and QoL following ST?

Research question 5: Do different surgical treatment modalities have an impact on both OHRQoL and QoL?

Study hypothesis 3: Comprehensive periodontal therapy (non-surgical therapy and surgical therapy, if required) in patients with type 2 diabetes is associated with an improvement in OHRQoL.

Research question 6: In patients with periodontitis and diabetes, does comprehensive periodontal therapy impact on OHRQoL?

Study hypothesis 4: Long term, regular SPC is associated with an improvement in OHRQoL and maintains the stability of periodontitis.

Research question 7: What impact does regular long-term SPC have on OHRQoL and QoL, when compared with irregular/ no SPC?

Research question 8: What is the prevalence of tooth loss in periodontitis patients enrolled in a long term SPC programme?

Research question 9: What is the prevalence of disease progression (as measured by CAL loss) in periodontitis patients enrolled in a long term SPC programme?

The overall structure of the thesis is set out in Table 3.

Table 3. Structure of Thesis

	Research Question	Study Design	Chapter
1.	What is the impact of NST on both OHRQoL and QoL?	Prospective, non-randomised, interventional clinical study	4
2.	What is the relationship between OHRQoL and QoL following NST?	Prospective, non-randomised, interventional clinical study	4
3.	What Is the impact of ST on both OHRQoL and QoL?	[redacted]	[redacted]
4.	What is the relationship between OHRQoL and QoL following ST?	[redacted]	[redacted]
5.	Do different surgical treatment modalities have an impact on both OHRQoL and QoL?	[redacted]	[redacted]
6.	In patients with periodontitis and diabetes, does comprehensive periodontal therapy impact on both OHRQoL and QoL?	Prospective, randomised controlled clinical trial	6
7.	What impact does regular long-term SPC have on OHRQoL and QoL, when compared with irregular/ no SPC?	Systematic review and meta-analysis.	7
8.	What is the prevalence of tooth loss in periodontitis patients enrolled in a long term SPC programme?	Systematic review and meta-analysis.	7
9.	What is the prevalence of disease progression (as measured by CAL loss) in periodontitis patients	Systematic review and meta-analysis.	7

Research Question	Study Design	Chapter
enrolled in a long term SPC programme?		

[redacted]

This PhD thesis therefore explores the different treatment modalities commonly used for periodontal therapy, and how these impact on OHRQoL and QoL. This theme is taken further by evaluating these treatments in conjunction with PROMs in a medically compromised diabetic population. The final investigative chapter presents the results of a systematic review and meta-analysis on our current knowledge of OHRQoL in long-term SPC, completing the periodontitis patient's journey.

4. TRIANGULATION OF NON-SURGICAL PERIODONTAL THERAPY, ORAL HEALTH RELATED QUALITY OF LIFE AND QUALITY OF LIFE.

4.1 Background

Periodontal diseases have been shown to have a considerable negative impact on reported oral health related quality of life (Needleman et al., 2004, Ng and Leung, 2006, Tsakos et al., 2010). Traditional views have often referred to periodontitis as a 'silent' disease however, due to evidence of its negative impact on everyday activities, this must now be challenged (Cunha-Cruz et al., 2007, Buset et al., 2016), and the focus now directed toward how daily life could change as a result of treatment(s) (Tsakos et al., 2006).

Traditional surrogate measures of periodontitis (such as probing pocket depths and bleeding on probing) may be used in conjunction with information from general health related quality of life (QoL) and oral health-related quality of life (OHRQoL) indicators to understand disease status and treatments in a more patient-centric manner (Slade et al., 1998, Ng and Leung, 2006). As such, a vast number of QoL instruments have been developed in the medical and dental fields in order to capture this information (Shanbhag et al., 2012, Graziani and Tsakos, 2020, Wong et al., 2021). One of these tools, the oral impacts on daily performance (OIDP), is a frequently used and validated OHRQoL measure used in dentistry (Riva et al., 2021).

The OIDP questionnaire, is an OHRQoL tool which concentrates on the measures of disability and handicap on the daily life of an individual (Adulyanon and Sheiham, 1997). The OIDP combines the oral impact (frequency and severity) on eight daily performances including physical, psychological and social, over the preceding time period. The questionnaire has been designed to attribute oral impacts with specific oral problems, thus may be used as a

generic OHRQoL measure in the form of the OIDP, or a condition-specific measure (CS-OIDP). To complement the information gained from OHRQoL questionnaires, global rating questions (single item ratings) have also been introduced. These direct questions ask participants to rate either general or oral health in categorical or visual manner (visual analogue scale) (Bennadi and Reddy, 2013).

Behaviour management, treatment of periodontitis, and a carefully designed long-term supportive care programme, are essential aspects of periodontal care to maximise tooth survival (Sanz et al., 2020). As part of the *second step of therapy* (Sanz et al., 2020), subgingival instrumentation (NST), has demonstrated consistent improvement in perceived OHRQoL in a number of studies (Saito et al., 2010, Nagarajan and Chandra, 2012, Shanbhag et al., 2012, Wong et al., 2012). A correlation between the phase of periodontal treatment and OHRQoL measures have also been reported, potentially demonstrating a sensitivity of these instruments in measuring change in periodontal status (Needleman et al., 2004, Saito et al., 2011, Makino-Oi et al., 2016).

The independent effect of periodontitis and its psychosocial consequences on the many variables that formulate QoL is an area that requires more investigation (Ng and Leung, 2006, Locker and Allen, 2007). The challenge is that the association of health and QoL is not clear. Cancer patients for example, do not report worse life satisfaction than healthy patients (Kreitler et al., 1993), furthermore, perspectives of QoL may change over time due to an individual's experience (Allison et al., 1997, Sprangers and Schwartz, 1999, Carr et al., 2001).

One frequently used QoL measure is the EQ-5D tool (EuroQol Group, 1990, Rabin and de Charro, 2001, Devlin and Brooks, 2017). The EQ-5D tools are a family of instruments which are used to describe and value health. The various instruments (e.g., EQ-5D-3L, EQ-5D-5L or EQ-5D-Y) are comprised of 5

dimensions (5D) regarding problems with mobility, self-care, usual activities, pain or discomfort, and anxiety or depression. The participant is asked to indicate his/her health state for each dimension, choosing from 3 levels (no problems, some problems or extreme problems) in the case of EQ-5D-3L. The second page of the questionnaire consists of the EQ-5D visual analogue scale (EQ-5D-VAS) which captures the participant's self-rated health, from, 'the best you can imagine' to the 'worst health you can imagine'. It is a quantitative measure (0-100) as judged by the respondent. The National Institute for Health and Care Excellence (NICE) recommends use of these indicators in healthcare research, particularly due to its simplicity and ease of use. Furthermore, it is an instrument that underpins economic evaluations, particularly in healthcare decision making (Devlin and Brooks, 2017).

The relationship between QoL and OHRQoL is unclear, and even after a number of years, how each is ideally measured is still at matter of intense scrutiny (Locker and Allen, 2007, Locker and Quinonez, 2011). Limited triangulation of OIDP with both global QoL measures and clinical measures have been investigated to understand how they inter-relate. It cannot be assumed that since periodontal therapy results in improved OHRQoL that this would also translate to a positive effect on QoL (Nagarajan and Chandra, 2012). Thus, the aim of the present study is to assess the relationship between the non-surgical treatment of periodontitis with OHRQoL and global QoL measures.

4.2 Aim

To assess the relationship between OHRQoL, QoL and clinical outcomes following non-surgical periodontal therapy (NST) in patients with stage III and IV periodontitis.

4.3 Methods

4.3.1 Study Population and Setting

The study was designed as a prospective case series. Participants were recruited from the Unit of Periodontology at the Eastman Dental Hospital and Institute, London, United Kingdom.

Inclusion Criteria

Patients meeting the following inclusion criteria were invited to attend:

i) Stage III or IV periodontitis (Tonetti et al., 2018), ii) ≥15 teeth iii) ≥15 sites with probing pocket depths (PPD) ≥4mm, iv) systemically healthy patients or those with controlled systemic disease.

Exclusion Criteria

Potential participants were excluded if: i) pregnant or lactating, ii) received periodontal therapy under local anaesthetic in the previous 12 months, iii) diagnosed with drug-induced gingival overgrowth, iv) uncontrolled systemic medical conditions including hepatic disease, renal disease, diabetes mellitus (with poor metabolic control), transmittable diseases, cancer or HIV, v) subjects not capable of providing informed consent or vi) participation in any other dental study concurrently.

4.3.2 Outcome Measures

The primary outcome measure was the mean change in OIDP score before (baseline, BL) and after non-surgical therapy, at reassessment (RA).

Secondary outcome measures were:

- Mean number of periodontal probing pocket depths (PPD) ≥5 mm at BL and RA, and change between time points

- Mean full mouth plaque score (FMPS) at BL and RA, and change between time points
- Mean full mouth bleeding score (FMBS) at BL and RA, and change between time points
- Mean index score of EQ-5D-3L at BL and RA and change between time points
- Change in responses at BL and RA to single-item questions:
    - 'How would you rate the quality of your life?'
    - 'How is your general health?'
    - 'How is your periodontal health (i.e., health of your gums)?'
    - 'To what extent have the problems you have experienced affected your life overall and your quality of life?'
- Correlations between PPD, FMPS, FMBS, OIDP, EQ-5D-3L at BL and RA, and change between time points.

4.3.3 Sample Size

A sample size of 82 subjects was calculated to detect a minimally important difference of 4.5 in the OIDP score before and after non-surgical therapy. A mean pre-treatment score of 7.7 (±8.4) and mean post treatment OIDP score of 4.5 (±6.5) were assumed based on previous findings (Tsakos et al., 2010). The required sample size was calculated to give a power of 90% at a 5% significance level. The calculation was performed for both the generic OIDP and CS-OIDP, and the higher estimate of the required sample size was used. To account for a 10% dropout and 10% non-compliance rate, 100 patients were recruited.

4.3.4 Study Operators and Procedures

Study operators were primarily postgraduate students specialising in Periodontology, at various levels of the 3-year training program. Clinicians were always supervised by an experienced periodontist. Procedures were carried

out in the Unit of Periodontology at the UCL Eastman Dental Institute and Hospital, London, UK.

A baseline detailed periodontal examination was performed by the responsible clinician, which included a six-point periodontal chart, FMPS and FMBS. Initial therapy typically included four to six visits comprised of oral hygiene instructions, gross professional mechanical plaque removal (PMPR) and more careful subgingival instrumentation (NST). NST was carried out using a combination of hand and ultrasonic scalers under local anaesthesia. At RA (minimum of 6-8 weeks following the completion of NST), all baseline parameters were re-taken. The study flowchart is shown in Figure 2.

Each clinician was responsible for determining the overall treatment plan and number of treatment appointments needed. No restriction was placed on any aspect of treatment, however the majority of participants had active treatment completed in two to four sessions.

4.3.5 Data Collection

Demographics

Following consent to participate in the study, an interviewer-administered questionnaire collected information on basic socio-demographic variables, which included age, sex and smoking habits.

Clinical Outcomes

A full mouth six-point periodontal charting was carried out and the number of PPD≥5 mm was counted. Additionally, full mouth bleeding on probing (BOP) and plaque were recorded at six sites per tooth at BL (prior to NST) and RA, which was approximately 6-8 weeks following NST.

Patient Reported Outcome Measure (PROM) Questionnaires

Each participant was asked to complete a number of self-administered questionnaires at BL and 6-8 weeks following NST. These were:

- Oral Impacts on Daily Performance – Modified version (Tsakos et al., 2001) *(*Appendix A*)*
- EQ-5D-3L (EuroQol Group, 1990) which included a visual analogue scale (EQ-5D VAS) (Appendix B)
- Single-item direct questions addressing OHRQoL and global QoL (Locker and Quinonez, 2011) (previously stated in Section 3.3.2) (Appendix A*)*

OIDP scores were used to assess generic OHRQoL. The questionnaire measured the oral impact on nine performances of everyday life; eating food, speaking clearly, cleaning teeth/dentures, carrying out physical activities, going out, sleeping/relaxing, smiling/ laughing, moods and contact with other people.

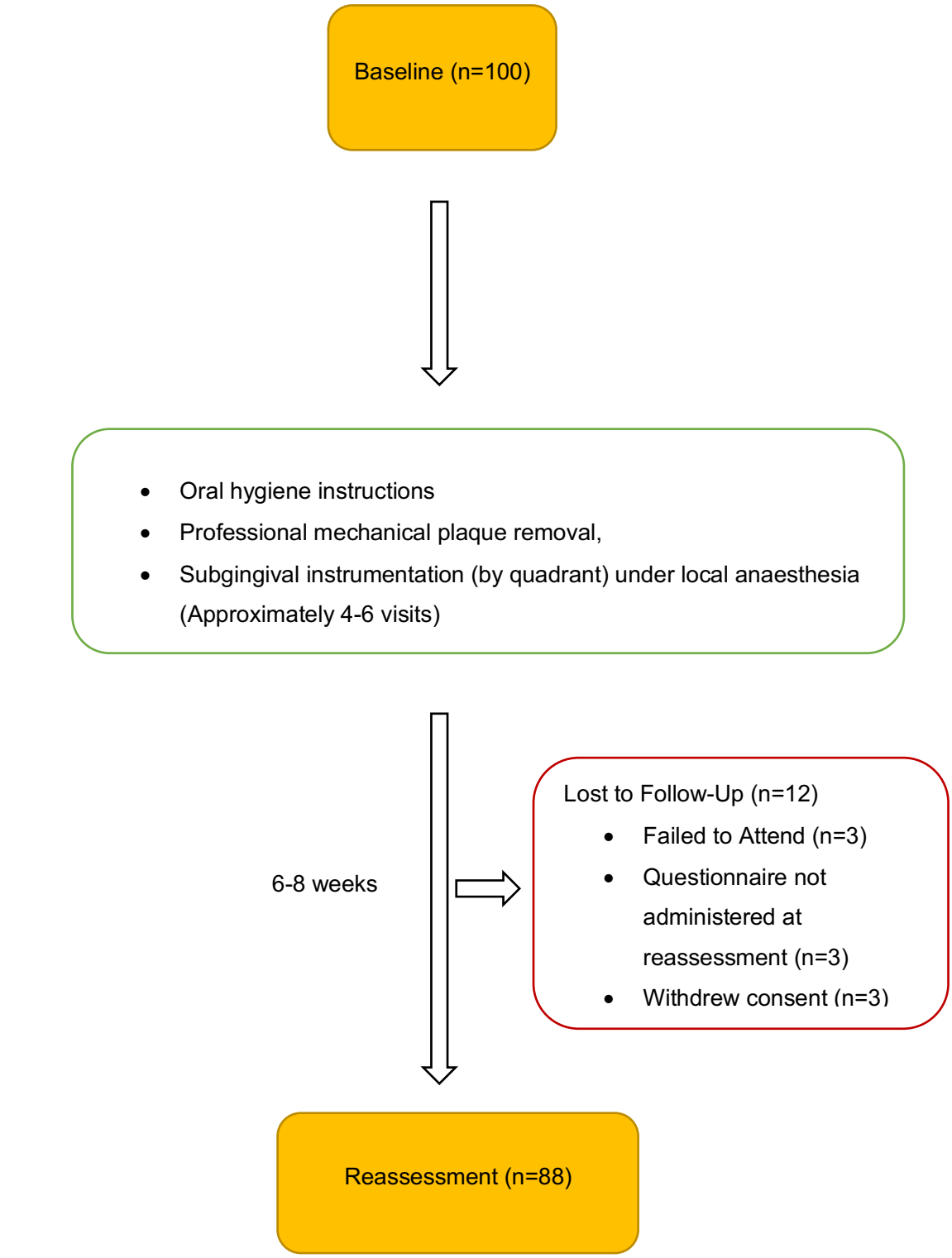

Figure 2. Flowchart of Study Design.

The overall OIDP score is the sum of each performance, divided by the maximum score (in this case 225), then multiplied by 100 to reach a percentage score. The score would thus be in the range of 0-100. The OIDP was designed also to attribute oral impacts to particular oral conditions, known as 'condition specific' OIDP (CS-OIDP). In this regard, a separate score was calculated (CS-OIDP) which only included those performance(s) where the oral impact was attributed to specific symptoms of periodontitis (e.g., tooth mobility, gingival recession). As with the OIDP, the sum of those particular performances were divided by the maximum score, and multiplied by 100 to reach a percentage score.

The EQ-5D-3L was used to assess global health related quality of life (EuroQol Group, 1990, Brooks, 1996). EQ-5D-3L has two elements, the first is a descriptive measure of the 5 dimensions (see Chapter 2.5.6) in regard to 3 levels of severity, and the second element requests the participant to rate overall health status by means of a visual analogue scale (EQ-5D VAS). The EQ-5D-3L for each person can be presented as a 'profile' which consists of five numbers (one for each dimension), with each number defined by the severity level reported (1= no problem, 2=some problems and 3 = extreme problems). A profile of 11111 for example, represents no problems on any of the five dimensions. This profile can then be converted to an index or value, utilizing published data sets for a specific population (Dolan, 1997, Dolan and Roberts, 2002). The index values according to the UK data set were calculated using a readily available online calculator (Economics Network). Index values are anchored at 0 (a state as bad as death) to 1 (a state of full health) (EuroQuol Group, 2022), thus an increase in index value over time represents an improvement in health state. The scale of the EQ-5D VAS is from 0 ('worst health you can imagine') to 100 ('the best health you can imagine').

Single global rating questions were administered in addition to the OIDP and EQ-5D questionnaires at BL and RA. The purpose of these was to provide a

'direct, appropriate assessment' of quality of life without the restriction of researcher chosen domains (Prutkin and Feinstein, 2002, Locker and Quinonez, 2011).

4.3.6 Statistical Analysis

The statistical analysis was performed using JMP®, version 9.0.1 (SAS Institute Inc., Cary, NC, 1989-2007). The distribution of the variables recorded in the study was assessed at BL and RA on a per protocol basis. These include demographic information, PROM scores (including global QoL outcomes), and clinical outcomes.

Differences between the BL and RA PROM scores and changes in global QoL outcomes (single-item questions) were assessed by Wilcoxon signed rank tests, comparing mean changes for each set of values. Specifically, changes in scores for the generic and CS-OIDP were calculated by subtracting the BL score from the RA score. Therefore, a negative change in score, represented an improvement in OHRQoL. A p-value of <0.05 for the net mean change was considered statistically significant.

Minimally important difference (MID) for both the OIDP and CS-OIDP scores from all participants were determined using the distribution-based approach (Revicki et al., 2006, Revicki et al., 2008, Tsakos et al., 2010). The standard error of measurement (SEM) was determined by multiplying the standard deviation of the mean OIDP/CS-OIDP score at BL by the square root of one minus the reliability of the OIDP/CS-OIDP (Tsakos et al., 2010, Masood et al., 2014). The value of the SEM was taken as the MID.

Effect size (η^2) was determined by subtracting the BL mean OIDP/CS-OIDP from the RA mean OIDP/CS-OIDP, and dividing by the group standard deviation at BL. Interpretation of η^2 was according to Cohen (1988) whereby benchmark values were 0.2 (small), moderate (0.5) and large (0.8).

Correlation coefficients (*r*) were calculated using the Spearman's rank test. Correlations between OIDP and CS-OIDP scores, with EQ-5D index scores and EQ-5D VAS scores were investigated. Additionally, a correlation coefficient was also calculated between clinical outcomes and PROM scores. A p-value of <0.05 was considered statistically significant. Correlations were further interpreted according to Taylor (1990) where, if $r \leq 0.35$ the correlation was 'weak', 0.36-0.67 was 'moderate', 0.68-0.90 was 'strong' and ≥0.90 was 'very strong'.

4.4 Results

4.4.1 Patient Demographics

100 patients (38 male and 62 female) were recruited for this study between February 2013 and July 2014. The Joint UCL/UCLH Human Research Ethics Committee granted approval for this study (07/Q0505/14). The study was conducted in accordance with the Helsinki declaration.

Baseline socio-demographics are shown in Table 4. Mean age of the participants was 49.2 (±9.7) years and 19% (n=19) were current smokers. 88 patients completed the study and the reasons for the drop-outs were as follows; failed to attend (n=6), questionnaire not administered at RA (n=3), withdrew consent (n=3). The mean age of the 88 participants that completed the study was 49.4 (±10.1) years and 17% (n=15) were current smokers. There were 53 females (60.2%) and 35 males (39.8%). All patients who completed the study received oral hygiene instructions and non-surgical periodontal therapy with local anaesthetic (as required) in 4-6 visits.

4.4.2 Clinical Outcomes

All clinical parameters showed a statistically significant improvement between BL and RA. The average time between BL and RA was 17.1 ±9.9 weeks (range 7.1- 74.0 weeks). Mean FMPS reduced from 54.4% (±22.3, 95% CI 50.0-58.9)

at BL, to 32.4% (±20.4, 95% CI 28.0-36.7) at RA which was statistically significant ($p<0.0001$). Mean FMBS also showed a statistically significant ($p<0.0001$) reduction from 40.5% (±23.8, 95% CI 35.8-45.2) at BL to 25.2% (±16.2, 95% CI 21.8-28.6) at RA. The mean number of PPD greater than or equal to 5mm (No. of PPD≥ 5mm) reduced significantly ($p<0.001$) from 52.4 (±24.5, 95% CI 47.5-57.3) at BL to 30.6 (±19.7, 95% CI 26.4-34.8) at RA. This is summarised in Table 5.

Table 4. Baseline Socio-Demographics

Demographics	
n	100
Mean Age (± SD)	49.2 (± 9.7)
Gender, n (%)	
Male	62 (62)
Female	38 (38)
Ethnicity, %	
Caucasian	72.7
Asian	7.1
Afro-Caribbean	8.1
Other	12.1
Smoking history, %	
Never	44
Current	19
Former	37

Table 5. Clinical Outcomes at BL (n=100) and RA (n=88)

Clinical Outcomes				
	Baseline	Reassessment	Difference	p-value
Full mouth plaque score, % (SD)	54.4 (22.3)	32.4 (20.4)	-21.3 (1.7)	<0.0001*
95% CI	50.0-58.9	28.0-36.7		
Full mouth bleeding score, % (SD)	40.5 (23.8)	25.2 (16.2)	-16.2 (1.9)	<0.0001*
95% CI	35.8-45.2	21.8-28.6		
No. of PPD ≥5 mm	52.4 (24.5)	30.6 (19.7)	-21.7 (1.9)	<0.001*
95% CI	47.5-57.3	26.4-34.8		

All values for baseline and reassessment are stated as means and standard deviations (SD). CI: confidence interval, PPD: periodontal pocket probing depth in millimetres (mm), *: statistically significant

4.4.3 Patient Reported Outcome Measures

OIDP and CS-OIDP

The mean OIDP score reduced (p=0.06) from 7.16 (±10.37, 95% CI 5.31 – 8.26) at BL to 5.51 (±7.6, CI 3.83 – 8.28) at RA, indicating an improvement in OHRQoL (Figure 3 shows change in OIDP by participant). Additionally, the mean CS-OIDP score (Figure 4, change in CS-OIDP by participant) also showed a statistically significant reduction (p=0.01) from 5.42 (±10.12, 95% CI 3.28 – 7.69) at BL to 3.0 (±6.80, 95% CI 1.65 – 4.45) at RA (Table 6).

No statistically significant changes were observed in the EQ-5D-3L score (0.01±0.01, p=0.32, 95%CI -0.1 – 0.014) or the EQ-5D-VAS scores (1.0±1.14, p=0.39, 95%CI -1.5 – 2.99) between BL and RA (Table 6).

Table 6. Patient Reported Outcomes at BL (n=100) and RA (n=88)

Patient Reported Outcomes				
	Baseline	Reassessment	Difference	p-value
OIDP Score	7.16 (10.37)	5.51 (8.30)	-1.65 (8.0)	0.06
95% CI	5.31 -8.26	3.83 – 7.28		
CS-OIDP Score	5.42 (10.12)	3.0 (6.8)	-2.42 (8.67)	0.01*
95% CI	3.28 – 7.69	1.65 – 4.45		
EQ-5D-3L	0.90 (0.13)	0.91 (0.12)	0.01 (0.01)	0.32
95% CI	0.86-0.91	0.88-0.93		
EQ-5D-VAS	78.8 (15.7)	79.8 (13.5)	1.0 (1.1)	0.39
95% CI	74.3-80.6	77.0-82.7		

All values for baseline and reassessment are stated as means and standard deviations (SD).
OIDP: Oral Impacts on Daily Performance, CI: confidence interval, CS-OIDP: condition specific OIDP, EQ-5D-3L: EuroQol questionnaire, EQ-5D-VAS: EuroQol Visual Analogue Scale

Figure 5. shows the proportion of respondents who recorded a negative impact attributed to periodontitis. At BL, the greatest proportion of respondents felt that smiling was negatively impacted by their condition (39%, n=39), followed by difficulty with cleaning their teeth or dentures (35%, n=35) and difficulty with eating (31%, n=31). At RA, these three domains remained the most frequently indicated, with 36.4% (n=32) registering a negative impact with smiling, 30.7% (n=27) with eating, and 28.4% (n=25) with cleaning their teeth. The greatest proportional reduction (10.4%) in respondents indicating a negative impact was seen in the emotional stability domain, followed by the ability to relax domain (7.4% reduction).

QoL

The mean EQ-5D-3L index value (Table 6) at BL was 0.90 (±0.13, 95% CI 0.86-.91) which minimally changed to 0.91 (±0.12, 95% CI 0.88-0.93) at RA. The mean change of 0.01 (±0.01) was not found to be statistically significant (p=0.32). Likewise, the EQ-5D-VAS mean score saw little change from 78.8 (±15.7, 95% CI 74.3-80.6) at BL to 79.8 (±13.5, 95% CI 77.0-82.7) at RA. The mean change of 1.0 (±1.1) was not found to be statistically significant (p=0.39).

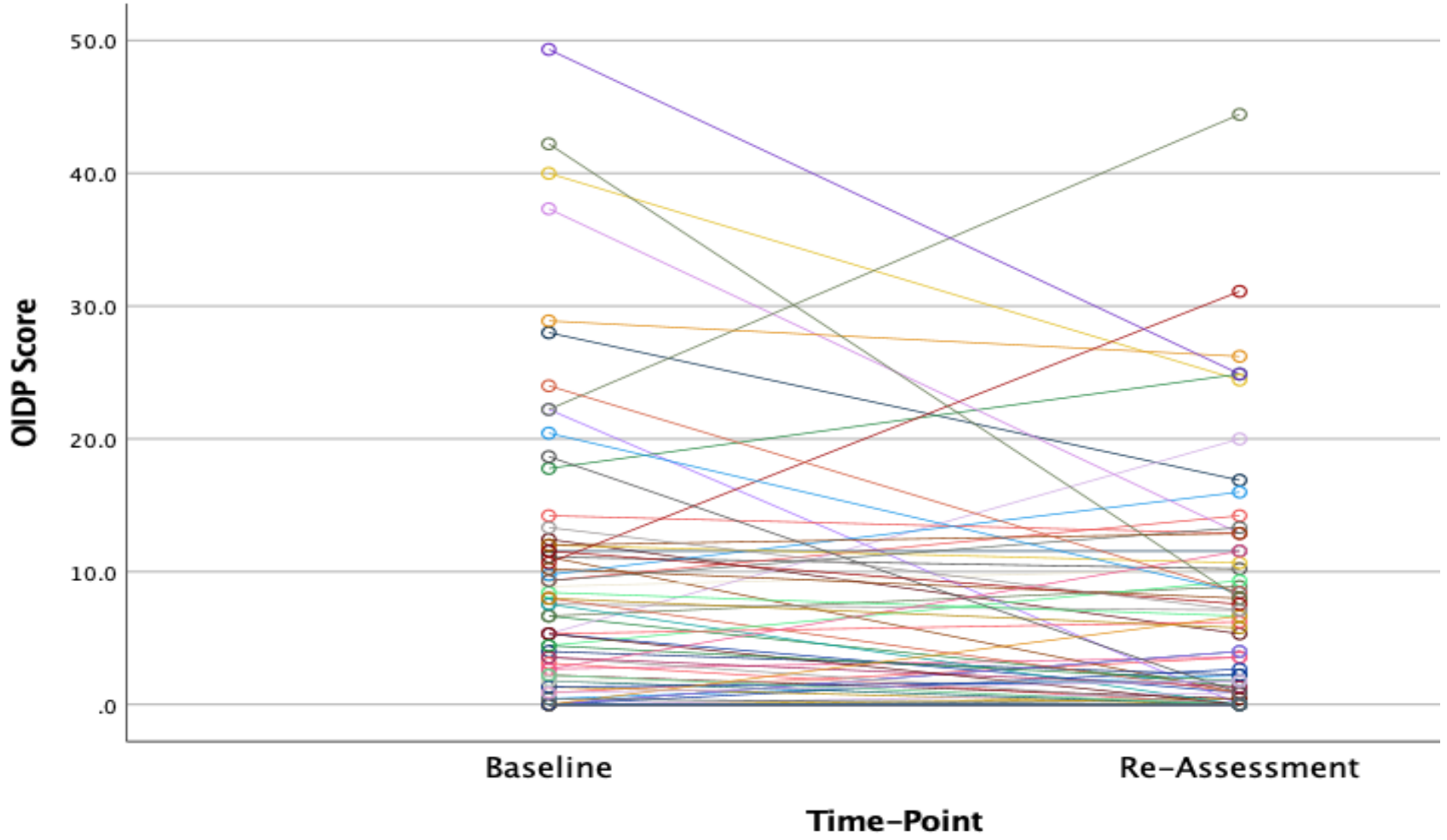

Figure 3. Line graph showing change in OIDP score between BL and RA by participant (n=88)

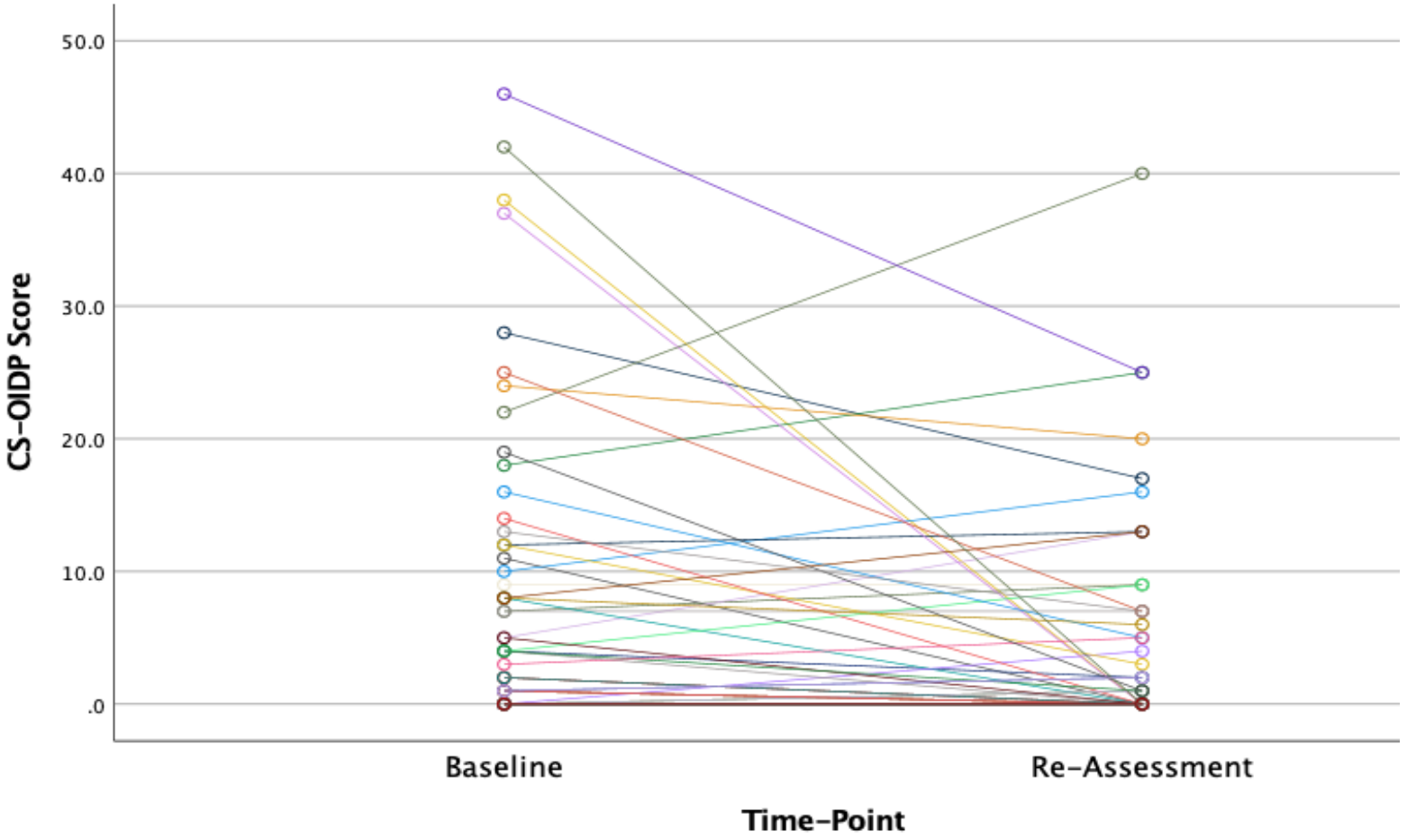

Figure 4. Line graph showing change in CS-OIDP score between BL and RA by participant (n

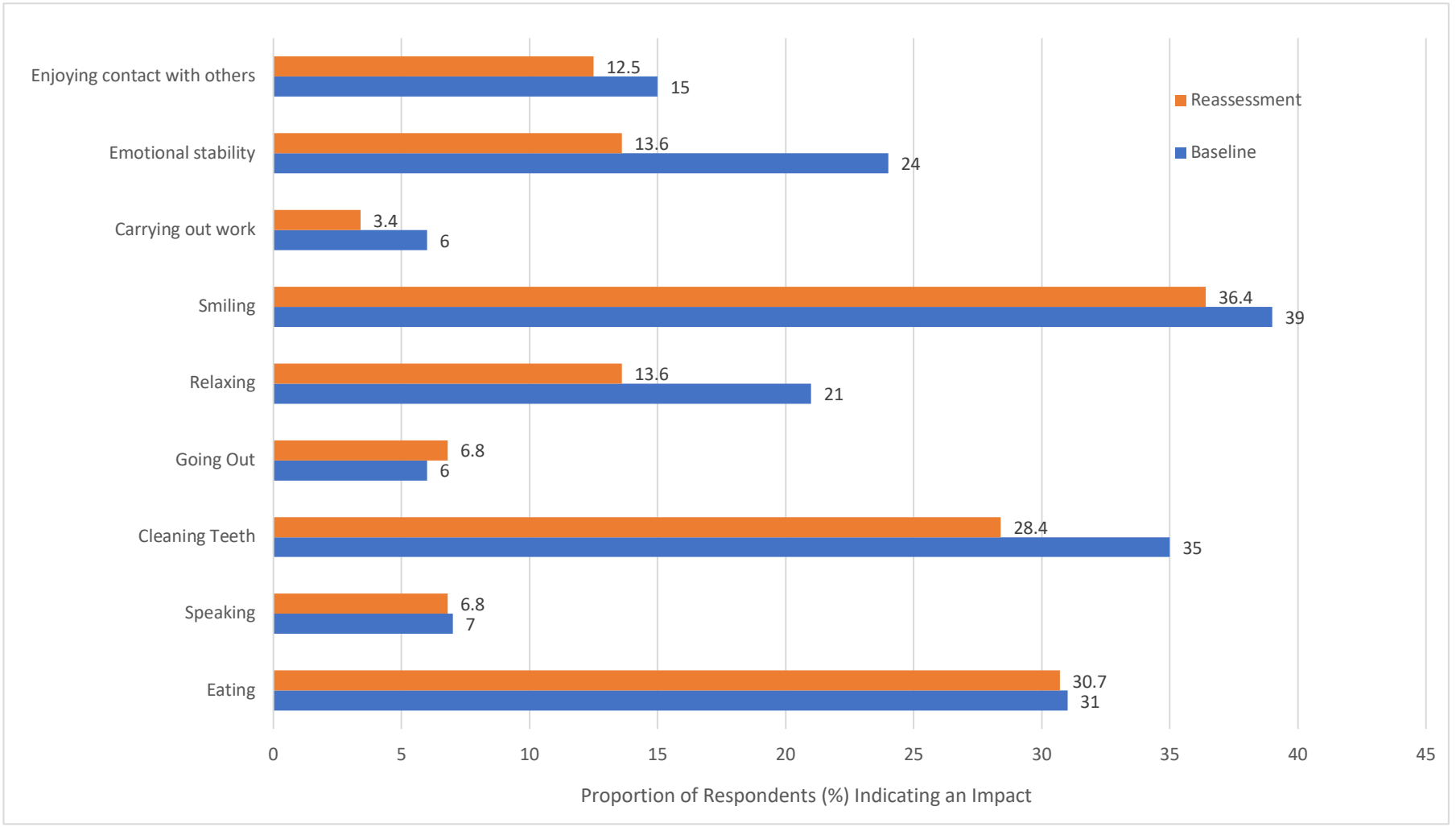

Figure 5. Recorded Impacts in CS-OIDP questionnaire at BL (n=100) and RA (n=88).

Frequencies reported by dimension and level (no problems, some problems or extreme problems) at BL and RA are shown in Table 7 and Table 8 respectively. At BL, one participant (0.6%) reported, 'extreme problems' for the anxiety/ depression dimension, whilst no other participant reported this level for other dimensions at either time point. At BL (Table 7), for those indicating, 'some problems', the association was with the pain/ discomfort dimension (n=35, 21.7%) and anxiety/ depression (n=30, 18.6%). At RA (Table 8), a similar pattern was seen for 'some problems', with reduced frequencies for pain/ discomfort (n=25, 15.5%) and anxiety/ depression (n=20, 12.4%).

Table 7. EQ-5D-3L frequencies by dimension and level at BL.

EQ-5D-3L (Baseline)					
	Mobility n (%)	Self-Care n (%)	Usual Activities n (%)	Pain/ Discomfort n (%)	Anxiety/ Depression n (%)
No Problems	92 (57.1)	97 (60.2)	92 (57.1)	63 (39.1)	67 (41.6)
Some Problems	6 (3.7)	1 (0.6)	5 (3.1)	35 (21.7)	30 (18.6)
Extreme Problems	0 (0)	0 (0)	0 (0)	0 (0)	1 (0.6)

Table 8. EQ-5D-3L frequencies by dimension and level at RA.

EQ-5D-3L (Reassessment)					
	Mobility n (%)	Self-Care n (%)	Usual Activities n (%)	Pain/ Discomfort n (%)	Anxiety/ Depression n (%)
No Problems	82 (50.9)	86 (53.4)	81 (50.3)	62 (38.5)	67 (41.6)
Some Problems	5 (3.1)	1 (0.6)	6 (3.7)	25 (15.5)	20 (12.4)
Extreme Problems	0 (0)	0 (0)	0 (0)	0 (0)	0 (0)

The frequencies were further dichotomised into, 'no problems' (included level 1/ no problems) or 'any problems' (included level 2/some problems and level 3/extreme problems). When comparing the frequencies for the two levels for each dimension between BL and RA, the difference was not found to be statistically significantly different for mobility (p=0.32), self-care (p=1.0), usual activities (p=0.08), pain/ discomfort (p=0.30) or anxiety/ depression (p=0.56).

Single-Item Questions

Responses to the single-item global question related to general health is shown in Figure 6. Responses were subsequently dichotomised into 'Good' (included 'good' and 'very good' responses) and 'Poor' (included, 'fair', 'poor' or, 'very poor' responses). Once dichotomised, there was no statistically significant change (p=0.72) from BL to RA (BL 80% vs RA 82.9%) for general health.

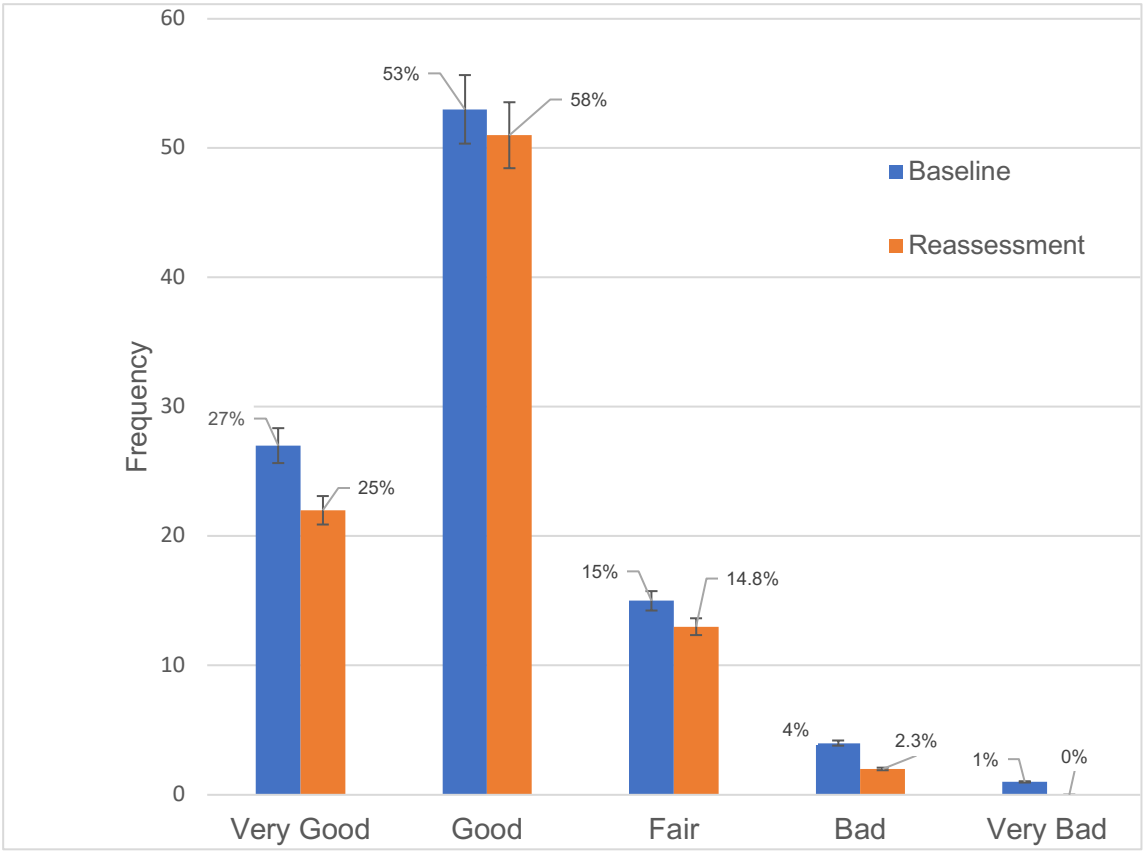

Figure 6. Responses to, 'how is your general health?' at BL (n=100) and RA (n=88).

Frequency responses to the question related to dental health is shown in Figure 7. Dichotomisation of responses into, 'Good' and 'Poor', showed a statistically significant change (p=0.005) in responses in the 'Good' category between BL (n=17, 17%) and RA (n=31, 35.2%), with change toward improvement in dental health.

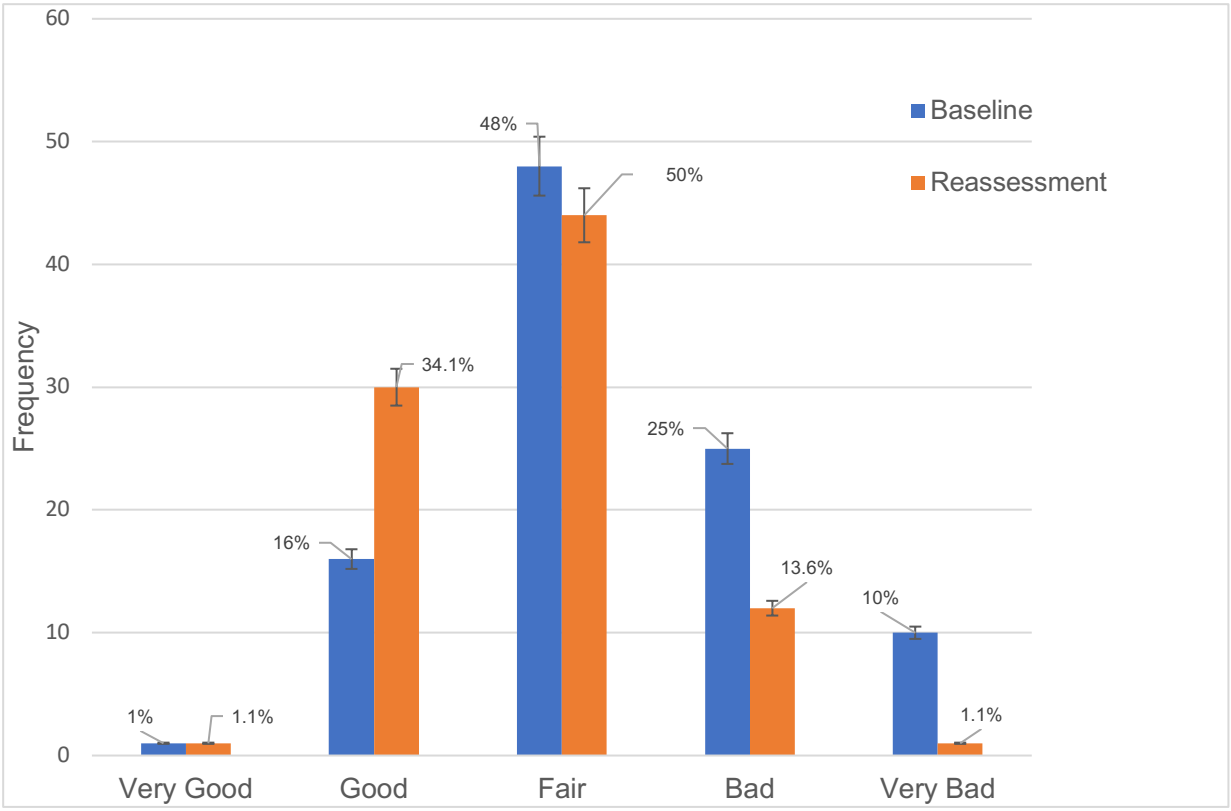

Figure 7. Responses to, 'how is your dental health?', at BL (n=100) and RA (n=88).

Periodontal health frequency responses are shown in Figure 8. The majority (n=75, 75%) of respondents felt that their periodontal health was, 'bad' (n=53, 53%) or very bad (n=22, 22%) at BL which reduced to 34.1% (n=30) at RA. Following dichotomisation, a statistically significant (p=0.0004) improvement was found toward the 'good' category, between BL (n=2, 2%) and RA (n=15, 17.1%).

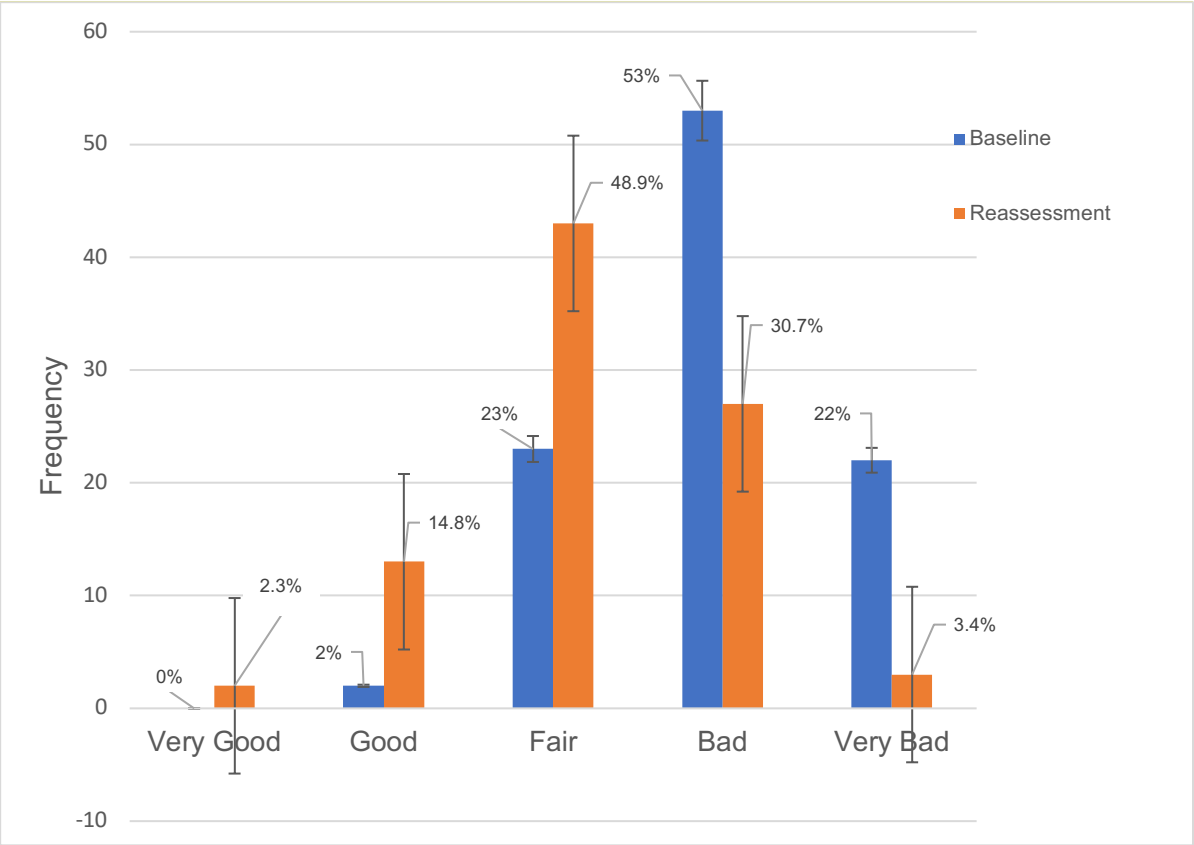

Figure 8. Responses to, 'how is your periodontal health?' at BL (n=100) and RA (n=88).

Figure 9, Figure 10 and Figure 11 show the responses to the questions, 'to what extent have you been bothered by the problems asked in the questionnaire?', 'to what extent has your life overall been affected by these problems?' and, 'to what extent have these problems affected your quality of life?' respectively. Over one third of respondents for being bothered by problems at both BL (n=35, 35%) and RA (n=30, 34.1%) was, 'a little' (Figure 9), whilst a reduction in the proportion being affected, 'a great deal' reduced from 16% (n=16) at BL to 10.2% (n=10.2%) at RA. Responses were dichotomised into, 'A Little', (included 'Not at All' and, 'A Little' categories) or 'Fair Amount' (included, 'somewhat', 'fair amount' and 'a great deal' categories. The proportion that was affected, 'A Fair Amount' was 51% (n=51) at BL which

reduced to 46.5% (n= 41) at RA. No statistically significant difference (p=0.59) from BL to RA regarding being bothered by the problems was detected.

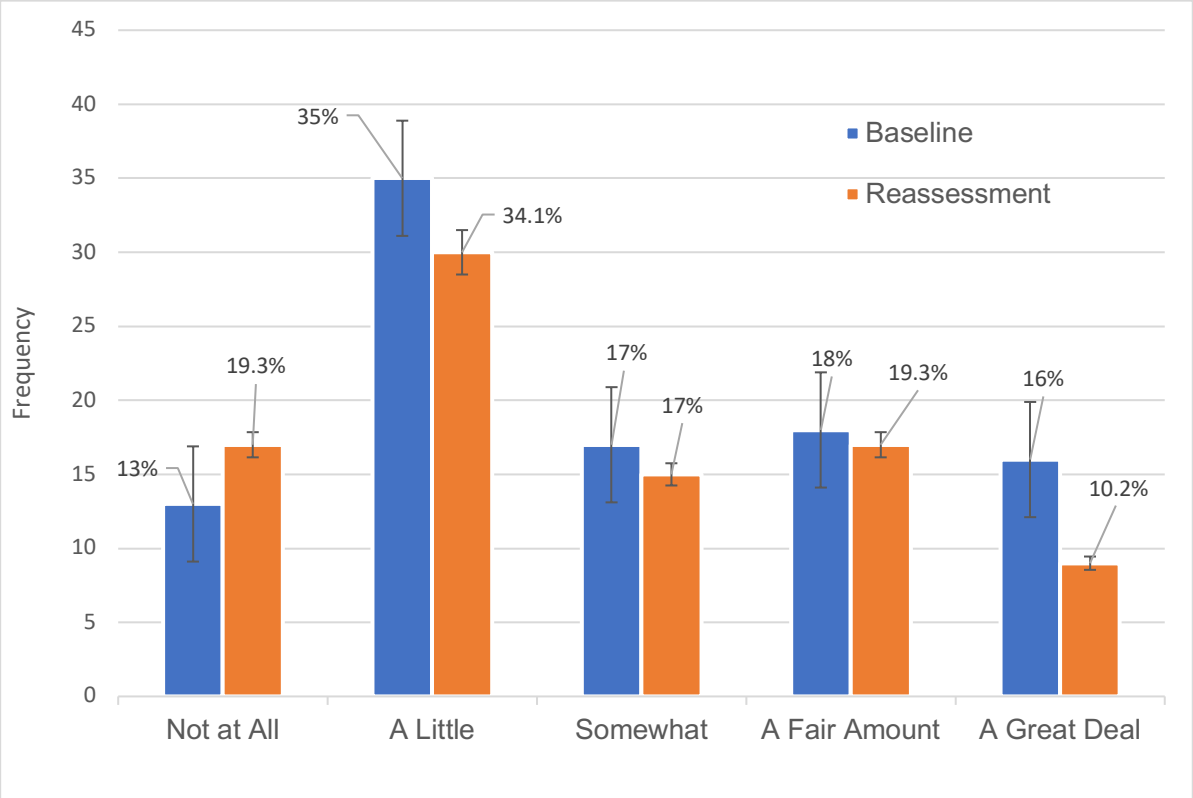

Figure 9. Responses to, 'to what extent have you been bothered by the problems asked in the questionnaire?' at BL (n=100) and RA (n=88).

Regarding the extent the participant's life overall had been affected (Figure 10), the greatest proportion of participants at BL said, 'not at all' (31%, n=31), whilst at RA, most participants indicated, 'a little' (39.8%, n=35). Following dichotomisation, the proportion of participants who were affected a 'fair amount' reduced from 41% (n=41) at BL to 28.4% (n=25) at RA, although this change was not found to be statistically significant (p=0.08).

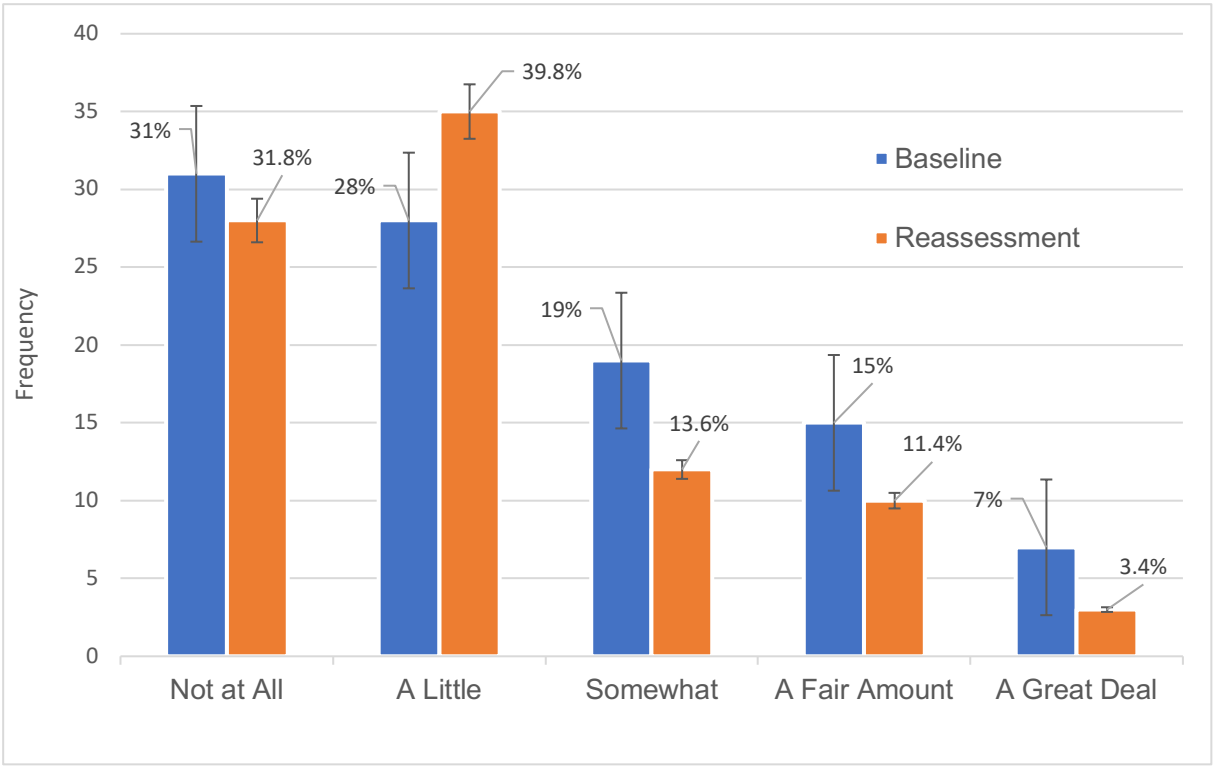

Figure 10. Responses to, 'to what extent has your life overall been affected by these problems?' at BL (n=100) and RA (n=88).

When asked to evaluate the extent to which these problems have affected the participant's quality of life (Figure 11), at BL, most respondents said, 'a little' (34%, n=34) whilst at RA this shifted to, 'not at all' (44.3%, n=39). Following dichotomisation, at BL 34% (n=34) of participants were affected a 'fair amount' whilst at RA this reduced to 19.3% (n=17). This change was found to be statistically significant (p=0.03).

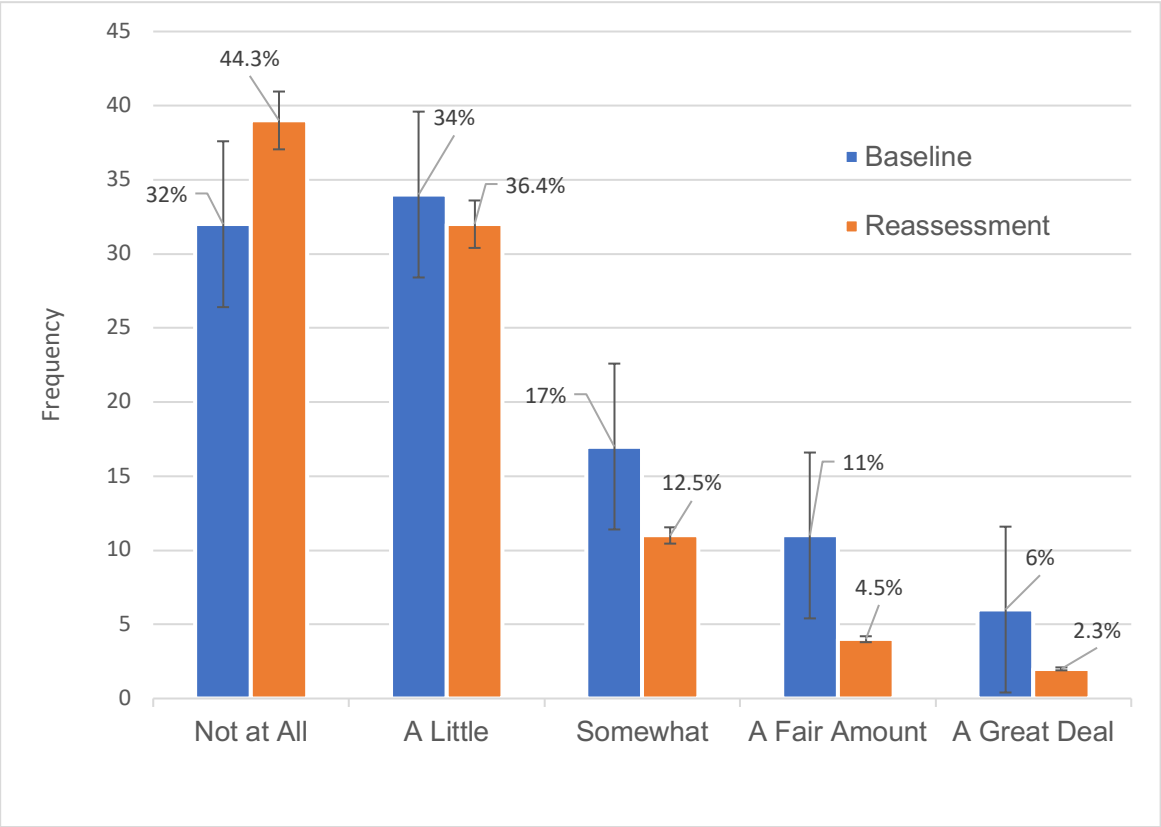

Figure 11. Responses to, 'to what extent have these problems affected your quality of life?' at BL (n=100) and RA (n=88).

Following treatment, participants were asked to rate their periodontal health. Figure 12 displays the responses. Encouragingly, 48.8% (n=42) felt their periodontal health, 'improved a lot', 46.5% (n=40) felt their periodontal health, 'improved a little', and 4.7% (n=4) felt it had 'stayed the same'.

Finally, participants were asked to rate their quality of life from BL to RA. The 6-point Likert scale (which ranged from, 'Excellent' to 'Very Poor') was further dichotomised into, 'Excellent' (included 'excellent', 'very good' and 'good') or 'Poor' (included, 'fair', 'poor' and 'very poor').

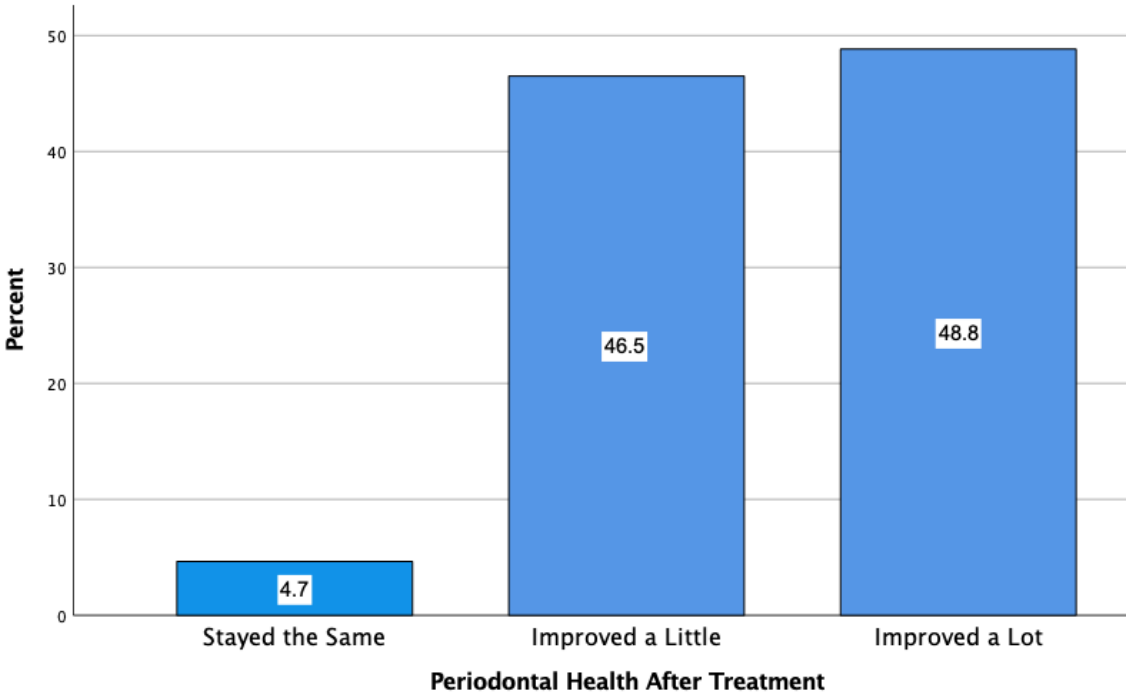

Figure 12. Self-Rated Periodontal Health Following Treatment (n=88).

When participants were asked to rate their quality of life (Figure 13), 40% (n=40) felt their quality of life was, 'very good', at BL, and this proportion slightly reduced to 37.5% (n=33) at RA. Only one participant at BL felt their QoL was, 'very poor', whilst this dropped to zero at RA. Following dichotomisation, there was a modest increase in the proportion of those in the 'Excellent' category (BL 83% vs RA 87.5%). This change was not found to be statistically significant (p=0.63).

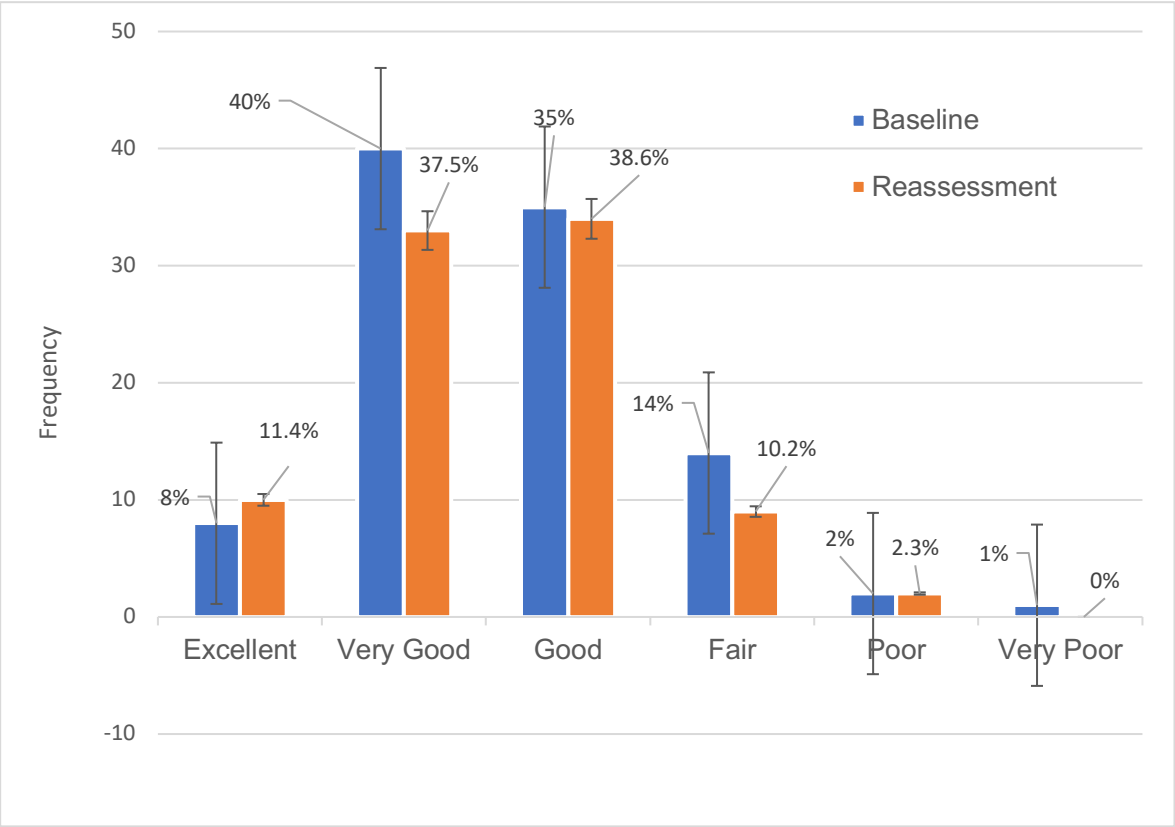

Figure 13. Responses to, 'how would you rate your quality of life?' at BL (n=100) and RA (n=88).

Correlations

Spearman's rank correlations of PROM outcomes in relation to No. of PPD≥ 5mm is shown in Table 9. At BL, weak to moderate (Taylor, 1990) statistically significant correlations were found between OIDP and EQ-5D-VAS (-0.36, p=0.0004) and EQ-5D-3L (-0.40, p<0.0001) but not with PPD≥5 mm (0.10, p=0.56). The negative correlation between OIDP score and EQ-5D-3L or EQ-5D-VAS might be expected, as a higher OIDP score (corresponding to a worse OHRQoL) was correlated with a lower EQ-5D-3L or EQ-5D-VAS score (worse QoL). CS-OIDP was weakly negatively correlated with EQ-5D-VAS (-0.31, p=0.0003) and EQ-5D-3L (-0.38, p=0.0005) but again, not with No. of PPD≥

5mm (0.10, p=0.54). EQ-5D-3L was not found to be statistically significantly correlated with No. of PPD≥ 5mm (0.004, p=0.84). There was a statistically significant moderate correlation found between FMBS and No. of PPD≥ 5mm (0.56, p=0.001).

At RA, there was a weak statistically significant correlation between OIDP and EQ-5D-VAS (-0.17, p=0.01) but not with EQ-5D-3L (-0.002, p=0.20) nor No. of PPD≥ 5mm (0.03, p=0.71). CS-OIDP was once again significantly correlated (weakly) with EQ-5D-VAS (-0.19, p=0.03) and EQ-5D-3L (-0.05, p=0.01) but not with No. of PPD≥ 5mm (0.05, p=0.44). EQ-5D-3L was not statistically correlated with No. of PPD≥ 5mm (0.01, p=0.96). A statistically significant moderate correlation was again found between FMBS and No. of PPD≥ 5mm (0.54, p<0.001).

The correlations of mean change in PROM scores and No. of PPD≥ 5mm are shown in Table 10. OIDP was not significantly correlated with EQ-5D-VAS (-0.01, p=0.80) nor No. of PPD≥ 5mm (-0.04, p=0.45) but there was a statistically significant weak negative correlation with EQ-5D-3L (-0.26, p=0.02). CS-OIDP also did not significantly correlate with EQ-5D-VAS (0.02, p=0.97) nor No. of PPD≥ 5mm (0.02, p=0.97), however demonstrated a statistically significant negative correlation with EQ-5D-3L (-0.31, p<0.0001). There was no statistically significant correlation found between EQ-5D-3L and PPD>5 mm (-0.04, p=0.45). FMBS and No. of PPD≥ 5mm were statistically significantly correlated also (0.56, p<0.001).

Table 9. Spearman's Rank Correlation Scores for PROM at BL and RA.

Correlations (Baseline)								
	EQ-5D-VAS		**EQ-5D-3L**		**PPD≥5 mm**		**FMBS**	
	r	*p-value*	*r*	*p-value*	*r*	*p-value*	*r*	*p-value*
OIDP	**-0.36**	0.0004*	**-0.40**	<0.0001*	0.10	0.56	0.03	0.81
CS-OIDP	**-0.31**	0.0003*	**-0.38**	0.0005*	0.10	0.54	0.04	0.74
EQ-5D-3L	**0.45**	0.0002*			0.004	0.84	0.15	0.15
EQ-5D-VAS			**0.45**	0.0002*	0.07	0.51	0.14	0.17
FMBS	0.14	0.17	0.15	0.15	**0.56**	0.001*		
Correlations (Reassessment)								
OIDP	**-0.17**	0.01*	-0.002	0.20	0.03	0.71	-0.03	0.80
CS-OIDP	**-0.19**	0.03*	**-0.05**	0.01*	0.05	0.44	-0.03	0.77
EQ-5D-3L	**0.48**	0.000003*			0.01	0.96	-0.2	0.87
EQ-5D-VAS			**0.48**	0.000003*	0.07	0.55	-0.11	0.33
FMBS	-0.11	0.33	-0.2	0.87	**0.54**	<0.001*		

r: Pearson's correlation coefficient, OIDP: Oral Impacts on Daily Performance, CI: confidence interval, CS-OIDP: condition specific OIDP, EQ-5D-3L: EuroQol questionnaire, EQ-5D-VAS: EuroQol Visual Analogue Scale, PPD≥5 mm: mean number of periodontal probing depths greater than or equal to 5 millimetres, FMBS: mean full mouth bleeding score,*: statistically significant.

Table 10. Spearman's Rank Correlation of change in PROM and PPD≥5 mm.

Correlations (Change of Score)								
	EQ-5D-VAS		**EQ-5D-3L**		**PPD≥5 mm**		**FMBS**	
	r	*p-value*	*r*	*p-value*	*r*	*p-value*	*r*	*p-value*
OIDP	-0.01	0.80	**-0.26**	0.02*	-0.04	0.45	0.15	0.18
CS-OIDP	0.02	0.97	**-0.31**	<0.0001*	0.02	0.97	0.02	0.83
EQ-5D-3L	0.20	0.07			-0.04	0.45	-0.03	0.79
EQ-5D-VAS			0.20	0.07	0.18	0.09	0.20	0.06
FMBS	0.20	0.06	-0.03	0.79	**0.56**	<0.001*		

r: Pearson's correlation coefficient, OIDP: Oral Impacts on Daily Performance, CI: confidence interval, CS-OIDP: condition specific OIDP, EQ-5D-3L: EuroQol questionnaire, EQ-5D-VAS: EuroQol Visual Analogue Scale, PPD≥5 mm: mean number of periodontal probing depths greater than or equal to 5 millimetres, FMBS: mean full mouth bleeding score,*: statistically significant.

4.4.4 Minimally Important Difference

The MID was calculated using BL and post treatment OIDP and CS-OIDP scores utilising the distribution-based method and is displayed in Table 11. The MID for OIDP was estimated at 4.70, with a small effect size of 0.16, and for

CS-OIDP was 4.58 with a small effect size of 0.24. 17% (n=15) of participants had a change in OIDP score which was greater than or equal to the MID, and 16% (n=14) showed a change in CS-OIDP score which was greater than or equal to the MID.

Table 11. Minimally important difference for generic and condition-specific Oral Impacts on Daily Performance for whole sample (n=88).

	OIDP	**CS-OIDP**
Mean score at baseline (SD)	7.16 (10.37)	5.42 (10.12)
Mean score at 12 months (SD)	5.51 (8.30)	3.00 (6.80)
Change (95% CI)	1.65 (-0.04, 3.33)	2.42 (0.58, 4.26)
p value within group	0.06	0.01
Minimally Important Difference (MID)		
Effect size	0.16	0.24
Standard Error of Measurement	4.70	4.58

4.4.5 Triangulation of OHRQoL, QoL and Clinical Outcomes

The difference in the scoring system of the OIDP questionnaire (where a high score translates to worse OHRQoL) and QoL measures (a low score translates to a worse QoL) means that a negative direction in regard to correlation may be expected.

My findings indicated that whilst there was a weak and significant negative correlation between OHRQoL (both OIDP and CS-OIDP) and QoL measures (EQ-5D-VAS and EQ-5D-3L) at BL (i.e., worse OHRQoL correlated with worse QoL), neither OHRQoL nor QoL were found to have a statistically significant correlation with clinical outcomes (as measured by number of PPD≥5 mm). At RA once again, there was a weak and statistically significant negative correlation between OHRQoL and QoL (only CS-OIDP with EQ-5D-3L and EQ—5D-VAS and OIDP with EQ-5D-VAS) but not with extent of periodontitis for either OHRQoL or QoL. Regarding the change in scores from BL to RA, the only correlation found was a weak negative correlation between QoL (EQ-5D-3L) and OHRQoL (both OIDP and CS-OIDP).

Thus, whilst OHRQoL and QoL have a statistically significant weak negative correlation, which implies that people with worse OHRQoL appear to also have worse QoL (or vice versa), neither OHRQoL nor QoL was statistically significantly related to extent of periodontitis.

4.5 Discussion

4.5.1 Key Findings

OHRQoL (generic and condition-specific) improved significantly following NST however, the same could not be concluded with respect to general QoL. Self-rated dental and periodontal health also improved significantly following NST, with most change seen in the ‘bad’ and ‘fair’ categories.

Regarding triangulation of OHRQoL, QoL and clinical outcomes, OHRQoL exhibited a weak negative correlation with QoL implying that individuals with worse OHRQoL also exhibited worse general QoL, however neither of these appeared to correlate with extent of unstable periodontitis (No. of PPD≥ 5mm).

The MID for OIDP was estimated to be 4.70 with a small effect size of 0.16 and was 4.58 for CS-OIDP with a small effect size of 0.24. Less than 20% of

participants experienced a change in OIDP and CS-OIDP scores above the MID.

4.5.2 Agreements and Disagreements with Other Studies

In agreement with a well-supported body of evidence (Suvan et al., 2020), this study demonstrated statistically significant improvements in clinical parameters following NST in the short-term. It can be expected that with time, further healing would occur (Badersten et al., 1984a, Cobb, 2002, Apatzidou and Kinane, 2004) and more sites of PPD≥5 mm would resolve. Additionally, with a properly designed supportive periodontal care programme and excellent patient compliance, favourable results can be maintained in the long term (Axelsson and Lindhe, 1981c, Axelsson et al., 2004b), with only a small proportion of patients experiencing tooth loss or disease recurrence/ occurrence (Leow et al., 2021).

OHRQoL assessed in the short- term improved following NST which agrees also with the majority of available evidence (Shanbhag et al., 2012, Khan et al., 2021, Wong et al., 2021). Two systematic reviews (Shanbhag et al., 2012, Baiju et al., 2017) reported that most studies found an improvement in OHRQoL following NST. Botelho et al. (2020), conducted a systematic review and was able to include seven studies which use the OHIP-14 questionnaire as part of the methodology. Whilst I cannot compare the results with my study (due to being a different PROM) an interesting finding was how the improvement varied according to time following NST. The meta-analysis found that the greatest improvement in OHRQoL was consistently found 3-4 weeks after NST, which then declined 6-12 weeks after therapy. This could mean the findings of the present study potentially under-estimates the impact that NST has on OHRQoL.

Different tools are used in the measurement of OHRQoL in the periodontal literature (e.g., OHIP-14, OIDP or GOHAI are the most commonly used), and so, there is limited available evidence to compare the magnitude of the results

found in my study. The mean reduction of OIDP score (3.9 ±0.8) and CS-OIDP (3.7 ±0.9) in the current study however, falls within (or very close to) the range reported by Tsakos et al. (2010) which was 2.5-4.4 for OIDP and 2.9-3.6 for CS-OIDP. Similar to my study, Tsakos et al. (2010) administered the reassessment questionnaire in a subset of stage III/IV periodontitis patients, however the time point following therapy was shorter, being four weeks (versus 6-8 weeks in the current study) following NST (D'Aiuto et al., 2004, Tonetti et al., 2007). Additionally, the treating clinicians were all specialist periodontists, and the examiner was trained and calibrated for study purposes, whereas in this study, the supervised trainees conducted both treatment and examinations.

In contrast, Pereira et al. (2011) assessed the impact of conventional periodontal treatment on mastication and found in a small group of participants (n=28) that there was a mean change in OIDP score of 9.93, which appears to be of much greater magnitude than the present study and that of Tsakos et al. (2010). The main similarity between this study and the current study is that the questionnaires were administered at approximately the same time points (45 days after NST in Pereira et al. 2011 and approximately 42-56 days in the present study). The diagnosis of chronic periodontitis, however, was based on participants displaying periodontal pockets in ≥4 sites on different teeth with a depth of ≥4 mm, which means this cohort of patients could potentially have had less severe disease than the current study. Furthermore, those participants requiring periodontal surgery, were excluded from the sample, which further implies that in this cohort of patients, periodontitis was resolved by guiding behaviour change, managing risk factors and NST (Sanz et al., 2020). I was not able to compare care-givers, as no description was available. For this cohort, the authors found a positive correlation ($r=0.506$, $p=0.007$) with mean PPD and OIDP score at BL, which was not observed in the present study. One reason for this could be OIDP total score both at BL and RA were very high (64.00 and 54.07, respectively) compared with the current study (9.2 and 5.3, respectively) and Pereira et al. (2011) assessed full mouth mean PPD, whereas

the current study looked at number of PPD≥5mm. The reason for this large discrepancy in OIDP score is unclear, particularly as the manuscript did not explain the way OIDP total score was calculated. The current study calculated OIDP score according to Adulyanon and Sheiham (1997). The quality assessment of Pereira et al. (2011) was found to be 'medium' according to a modified version of the Newcastle-Ottawa scale (Shanbhag et al., 2012), although it is unclear exactly what this was attributed to (data not given), Finally, the OIDP questionnaire looked at eight aspects of daily life (rather than nine in the present study), with the additional performance being, 'going out'.

Another study (Santuchi et al., 2016), which compared quadrant debridement (Q-SRP) with full mouth disinfection (FMD) in 90 patients, did not administer questionnaires before and after therapy, but assessed OIDP 30 days and 180 days following NST. Median OIDP score at 30 days was 9.50 and 10.0 for FMD and Q-SRP respectively, which appears similar to BL values in the current study. At 180 days, median OIDP score was 8.0 and 4.0 for FMD and Q-SRP respectively. The Q-SRP score at 180 days was similar to the mean RA score (5.3), in the present study, with the latter however being at a shorter follow-up time. Although this study only assessed OIDP post treatment, it is interesting to note the reduction in OIDP score (representing an improvement in OHRQoL) over time, which conflicts with the results of a recent systematic review (Botelho et al., 2020), which showed that OHRQoL slightly reduced 6-12 weeks after therapy, when compared to 3-4 weeks after. The authors were not able to find a statistically significant difference in OHRQoL between these two post-therapy time points for either FMD or Q-SRP.

My study did not find an association of OHRQoL nor QoL with the number of deep probing depths (≥5 mm) at BL or after NST. This finding is not unique, as there is significant heterogeneity amongst the literature (Buset et al., 2016), with some studies finding increasing impact with greater disease severity or extent (Bernabe and Marcenes, 2010, Pereira et al., 2011) and others not (Lawrence

et al., 2008, Marino et al., 2008, Saito et al., 2010). The difference in results of the studies may be attributed to the heterogeneity in regard to selection criteria, sample sizes, clinical assessments and OHRQoL tools utilised in each study. A threshold of PPD ≥6 mm may also have been a consideration with regard to outcomes of therapy (in contrast to PPD≥5 mm). It could be argued that this threshold represents severe disease which is at greater risk of disease progression (Matuliene et al., 2008), particularly as surgical interventions are recommended at this level (Polak et al., 2020, Sanz et al., 2020, Sanz-Sanchez et al., 2020). The choice of PPD≥5 mm however was selected in context with consideration of ideal treatment outcomes (i.e., PPD<4 mm, absence of suppuration and a low proportion of sites which bleed on probing) presented in a number of European consensus conferences (Sanz et al., 2015, Tonetti et al., 2017b, Sanz et al., 2020).

QoL did not significantly change following NST in the current study. We were unable to find any studies assessing QoL before and after periodontal therapy. Additionally, we did not find a statistically significant corelation between QoL and extent of disease (No. of PPD≥ 5mm). Two recent systematic reviews have looked at QoL and periodontal diseases (Buset et al., 2016, Haag et al., 2017), and from these, it was highlighted that there are a lack of studies to support an association of QoL and periodontitis. In the most recent systematic review (Haag et al., 2017), seven studies were identified that investigated the association between QoL and gingivitis/periodontitis with conflicting findings. Three out of these seven studies did not find an association between gingivitis/ periodontitis and QoL, although one population study based (n=14,231) based on the Korean National Health and Nutrition Examination Survey (2007-2009) found periodontitis was associated with worse impacts on usual activities when compared with respondents without periodontitis (Sim, 2014). The authors of the systematic review highlighted clear methodological differences between included studies, with the authors emphasising that different case definitions

were used with mostly convenience samples determining study size (Haag et al., 2017).

One cross-sectional study from Australia (Brennan et al., 2007) used the EuroQol questionnaire to assess the impact of periodontal conditions (gingivitis and periodontitis) on QoL in 709 participants. The authors found that both gingivitis (n=33) and periodontitis (n=80) had an impact on a number of dimensions of QoL, but particularly that both PPD≥6 mm and loss of attachment ≥6mm (LOA≥6 mm) had a negative impact on the pain/discomfort dimension of the participants (25.8%, and 22.5% of people, respectively). Additionally, those that reported impact, experienced the pain/ discomfort for at least one third of the time (49.4% of the time for PPD≥6mm, and 37.5% of the time for clinical attachment loss ≥6 mm). Gingival recession ≥6 mm, PPD>6 mm and clinical attachment loss ≥6 mm also impacted on anxiety/ depression in approximately 10% of cases.

One recent study (Moghadam et al., 2015), conducted a population-based study (n=700) in Iran, and found a negative association between periodontitis and quality of life, which agrees with earlier studies (Reisine et al., 1989). Participants in this study were categorised 'healthy', 'gingivitis' or 'periodontitis' following a periodontal assessment (6-point periodontal chart). Periodontal probing depth was not included in the criterion for a diagnosis of periodontitis, however CAL>5 mm was. QoL was assessed using the WHO quality of life questionnaire (WHOQOL-BREF) and whilst there was trend of a worse QoL in the periodontitis group (when compared with the healthy and gingivitis groups), it is unclear if this difference was statistically significant.

The MIDs of 4.58 and 4.70 for OIDP and CS-OIDP respectively, are in line with that found in another study (Tsakos et al., 2010) who found the MID to be in the range of 5 scale points. Due to different domain assessments, I was unable to compare MID with other frequently used PROMs (e.g., OHIP-14) in periodontology. Furthermore, it is suggested that despite using the same

questionnaire, it should be expected that the MID is different, depending on the population and/or intervention carried out (Revicki et al., 2008).

The indication that less than 20% of participants experienced a change in PROMs score greater than or equal to the MID should be interpreted with caution. The calculation of the MID using the distribution-based approach is conducted at group level and reflects what might be considered a moderate to large effect (beyond the variation of the test) (Troosters, 2011), therefore, the proportion of individuals reaching the threshold of the MID could be an underestimation of those who actually felt a benefit.

4.5.3 Strengths and Limitations of the Study

This study is the first to assess health-related QoL, OHRQoL and clinical parameters following NST. A strength of this study is the sample size, whereby we were able to recruit and retain the minimum number required (according to the sample size calculation) to potentially minimise or avoid the risk of a type 1 error for the primary outcome. As such, my study was able to corroborate previous findings in regard to non-surgical therapy before and after treatment, and additionally provide novel and unique information in regard to how QoL relates to OHRQoL. No statistically significant difference in QoL was detected after NST which could be a true effect or could be attributed to a sample size based on OHRQoL. Thus, the sample size may not have been sufficiently large to detect a difference (if there is one) or the QoL instrument may not be sensitive enough to detect a difference in clinical changes of periodontitis.

Participants for this study were recruited from those referred to a dental hospital clinic with stage III/ IV periodontitis, therefore the patient cohort and level of disease are reasonably representative of patients referred for specialist care, however, may not be representative of those with severe disease who are managed in primary care/ general dental practice.

A number of different clinicians of varying experience levels were involved with this study. These clinicians were not calibrated or standardised in any regard therefore clinical measure of periodontitis, plaque and bleeding scores were largely left to the discretion of the individual clinician (although supervision by a qualified instructor was always present). Furthermore, no restriction was placed on the number of treatment sessions, length of time of each session nor instruments used. Although clinicians were not standardised, this may translate to a more generalisable study to clinical practice.

This study, being a prospective case series, had no control group, as such comparisons could only be drawn before and after treatment. This lack of control group however, is in line with other studies assessing non-surgical therapy and PROMs (Baiju et al., 2017), and one method to address this might be to delay treatment in the control group, however ethical issues may arise, particularly for patients with the most severe forms of periodontitis (stage III/IV). A consequence of this, is that no conclusive evidence can be provided in terms of effectiveness of NST in the improvement of OHRQoL or QoL. The magnitude of change in the OIDP score (-3.9) and CS-OIDP score (-3.7) in this study, is consistent with another study (Tsakos et al., 2010) who found a change of -3.2 for both generic and CS-OIDP in a study of 45 severe periodontitis patients following NST. This suggests that the findings of this study are representative of a true effect size for a moderate-severe periodontitis population.

The proposed follow up of a minimum of six to eight weeks in this study was relatively short. In reality, the majority of patients were reassessed following a much longer period of time (mean of 17 weeks) which might be seen as beneficial for healing, as long as excellent levels of oral hygiene are maintained. Although the majority of healing after non-surgical therapy occurs within the first 3 months, further healing can occur after this period (Badersten et al., 1981). Thus, the benefits of the non-surgical intervention may have had greater impact

on clinical and quality of life outcomes with a greater follow up period. In this study however, it is likely that oral hygiene fluctuated between the completion of NST and RA (FMPS 32.4 ±20.4%), thus reducing the benefit a longer period of healing. The implications for future research would therefore be to include longer follow-up periods, with oral hygiene closely monitored (and inclusion of SPC appointments where necessary) ideally beyond 6 months. Additionally, for clinical practice, a longer healing period after NST would be recommended to allow the majority of healing to occur and possibly have greater impact on patient-centred outcomes.

4.5.4 Implications for Practice and Policy

This study has demonstrated that in patients with stage III/IV periodontitis, OHRQoL improves in the short-term following NST. The implications of this on daily clinical practice is that patients can expect not only clinical benefits (with regard to clinical measures of periodontitis) but an improvement in the magnitude of impact on a variety of everyday life activities. This is particularly important for those patients unsure about proceeding with NST.

Additionally, health-related QoL research confirms the negative impact of periodontitis on both OHRQoL and QoL, and as this study confirms, subsequent improvement in OHRQoL, highlights the more widespread benefit to the patient above and beyond clinical outcomes. This research would enable policy-makers to make evidence-based decisions to channel greater funding toward national public health services delivering NST, but also provide additional education, resources and access to care for those in the population who traditionally would not seek treatment.

Although the present study did not find a statistically change in QoL before and after treatment, it should be considered that a correlation between OHRQoL and QoL was found, and greater funding to further explore QoL and

periodontitis treatments should be a priority considering the potential intangible benefits to the patient.

4.5.5 Implications for Further Research

The periodontal literature displays a variety of definitions and clinical parameters used to define periodontitis, which made comparing study populations difficult. Additionally, although some OHRQoL tools are more frequently used in periodontal research (i.e., OHIP-14 and OIDP), when different tools are used, this limits the comparability due to a different focus on domains explored and scoring systems. Therefore, future research would benefit from using a standard definition of periodontitis (Tonetti et al., 2018), and reaching a consensus (with transparent reasoning) on the OHRQoL tool(s), if one exists, which is most insightful to determine impacts of periodontitis and its treatments on everyday life, perhaps leading to the development of a new OHRQoL tool specifically for periodontitis.

QoL research in periodontitis patients is extremely limited, with very few studies exploring a possible association (Haag et al., 2017). To the best of my knowledge, this is the first study exploring the relationship between QoL and non-surgical periodontal therapy. Whilst the current study did not find a statistically significant change before and after NST, nor a correlation with the number of PPD≥5 mm, this does not exclude the possibility that there is a relationship between QoL and periodontitis (and its treatment) severity and/ extent. Further research in stage III/IV periodontitis patients with a large sample size would be essential in determining a relationship between QoL and periodontal therapeutic interventions (if any), with an aim to estimating a minimally important difference. In order to clarify the strength of relationship between OHRQoL and QoL and assess complementary information, both types of questionnaires should be included.

There was inconsistency on the most suitable time points to administer both OHRQoL and QoL questionnaires, with the majority of studies choosing an endpoint of up to 3 months following therapy. Future research should ideally include a greater number of time points for administration of the questionnaires in order to capture both positive and negative changes in the patient journey following an intervention. This would enable clinicians to best inform patients on what to expect following treatment with approximate time scales. Furthermore, the need for additional advice and support could be anticipated at time points with the greatest negative impact.

Lastly, studies exploring OHRQoL and QoL in periodontitis patients mostly have short follow-up times (up to 3 months), which gives no information on the impact of NST in the long term and/or during supportive periodontal care (SPC). Future research on OHRQoL/ QoL following therapeutic interventions should consider extending the length of follow-up (ideally a minimum of 12 months after NST) and include assessment during SPC.

4.6 Conclusions

This study has shown that following NST, patients with stage III or IV periodontitis can expect to experience improved OHRQoL, however a concomitant improvement in QoL cannot be assumed. The study found a statistically significant correlation of OHRQoL and QoL following NST but not with extent of disease.

Self-rated dental and periodontal health improved significantly following initial periodontal therapy.

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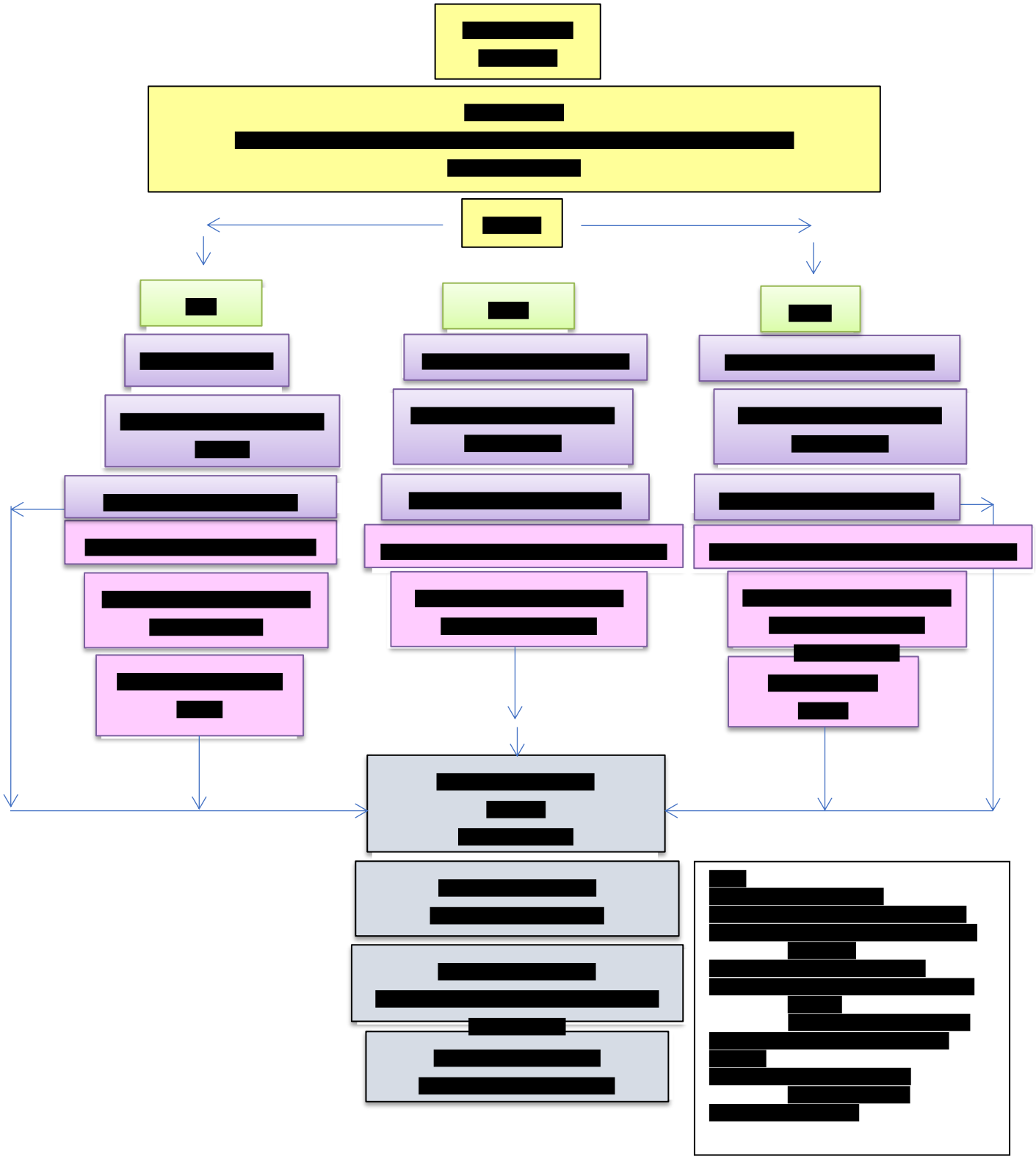

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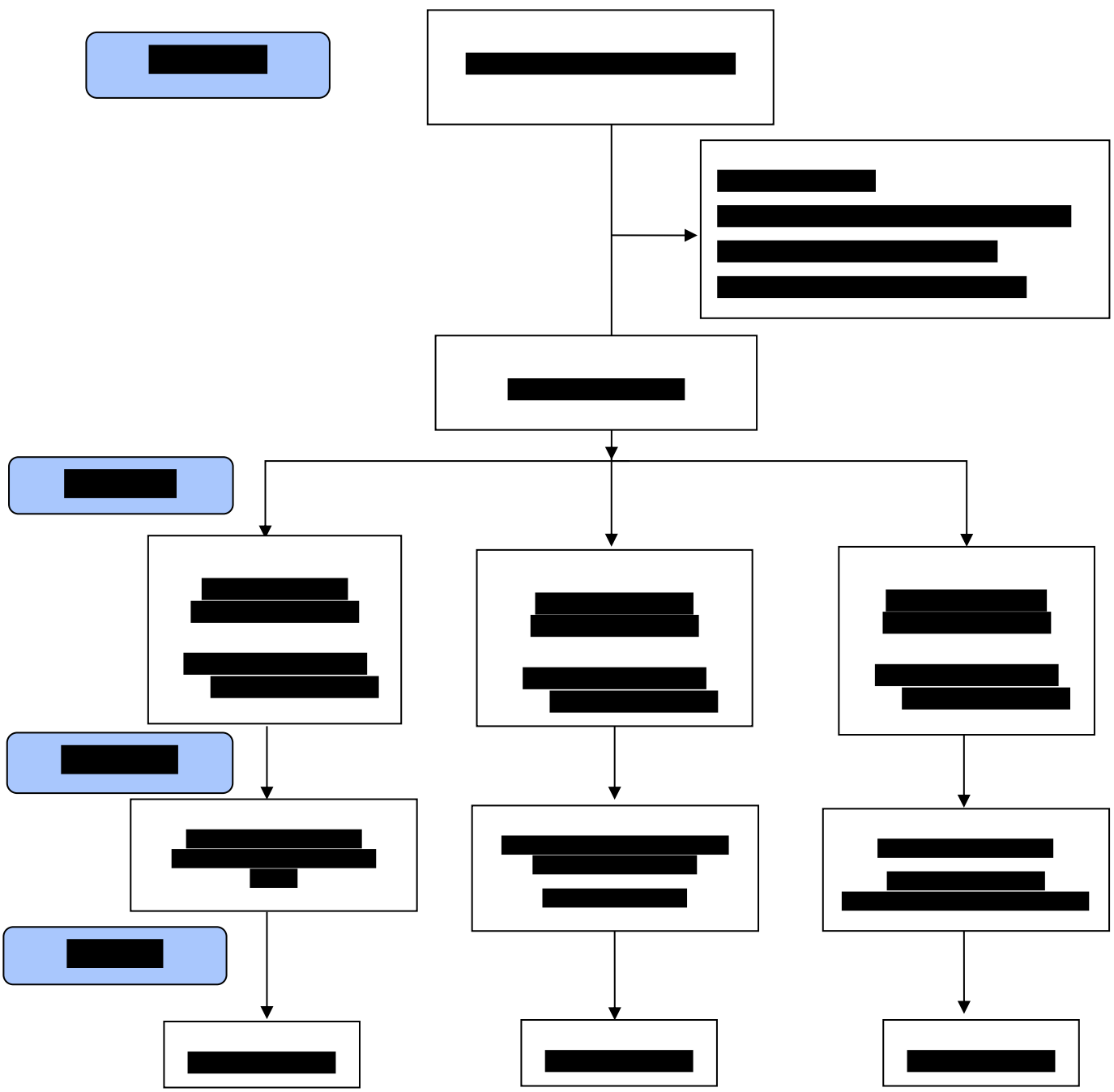

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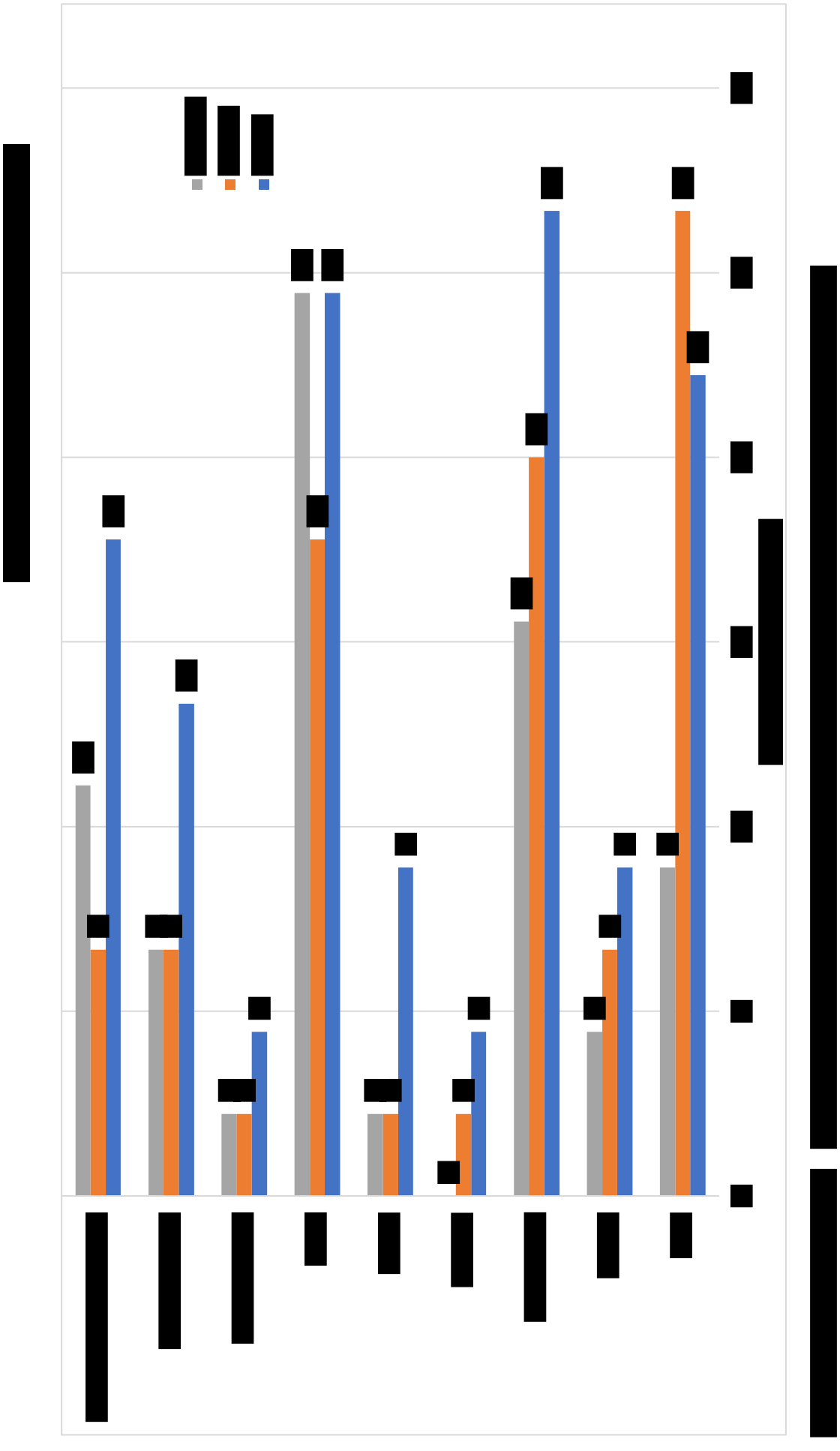

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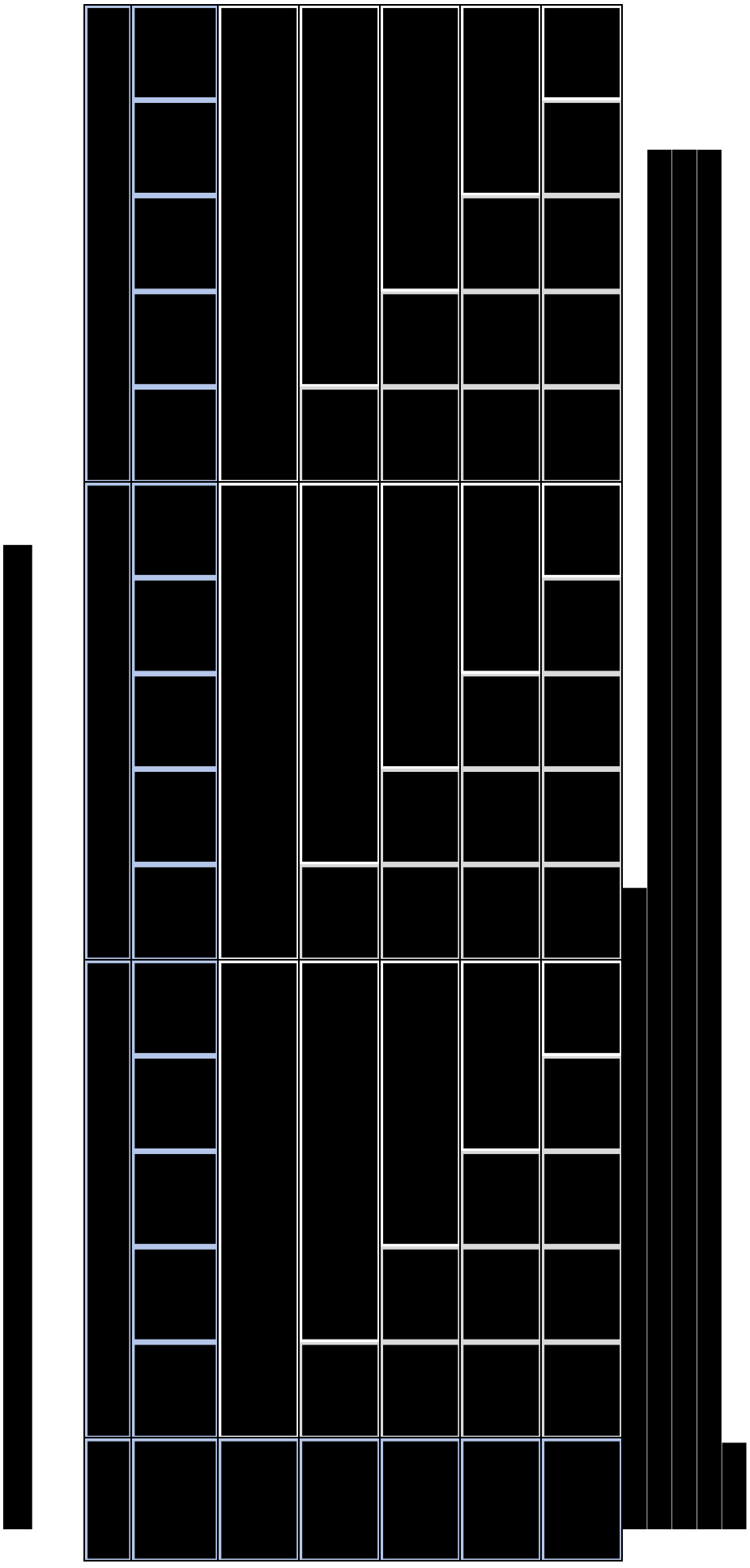

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6. IMPACT OF TREATMENT OF PERIODONTITIS ON PATIENT REPORTED OUTCOME MEASURES IN A DIABETIC POPULATION. A RANDOMISED CONTROLLED TRIAL.

6.1 Background

6.1.1 Patient Reported Outcomes in Diabetic Individuals

Health-related quality of life (HRQoL) assesses the effect of chronic diseases (and their management) on the everyday life of an individual. Diabetes has been shown to negatively affect HRQoL (Wong et al., 2013, Hsieh et al., 2023). According to one systematic review which included 26 studies (Wong et al., 2013), patients with diabetes had almost double (OR 1.82, 95% CI 1.63-2.04) the odds of negative impacts in activities of daily living (e.g. bathing, dressing, eating) when compared with individuals without diabetes. Mobility was also negatively impacted, with an odds ratio of 1.71 (95% CI 1.53-1.91) when compared with individuals without diabetes. These results have been further re-enforced with the retrospective, cross-sectional analysis of the NHANES data (2009-2014), whereby the authors found that patients with diabetes to have worse physical function (adjusted OR 2.49, 95% CI 1.91-3.25) based on 16,159 participants (Hsieh et al., 2023). It should be noted however that results may not solely be due to having diabetes, as shared risk factors with other chronic conditions could also contribute.

The prevalence of oral complications in patients with diabetes is high, and the prevalence of severe forms of periodontitis is almost 50% in patients with diabetes in the UK (White et al., 2012) . One cross-sectional study of 764 of patients with type 2 diabetes in Denmark (Verhulst et al., 2019b) found that more than one third of participants (37%) had self-reported xerostomia, whilst pain in the mouth (15%) and bad breath (12%) were also frequently experienced. General health-related QoL was assessed using the Dutch version of the 36-item short-form health survey (SF-36) and results found

impaired general health-related QoL in patients with type 2 diabetes, as reflected in generally lower concept scale scores when compared to the general population of Amsterdam and the Netherlands. Additionally, oral health-related quality of life (OHRQoL) was assessed using the Dutch version of the Oral Health Impact Profile questionnaire (OHIP-NL14). The authors found that OHRQoL was negatively impacted by pain in the mouth, xerostomia and bad breath and overall self-reported periodontitis patients had worse OHRQoL with a mean score of 2.6 ±4.7, compared with those without periodontitis (0.8 ±3.4). Thus, it is important to recognise oral complications, including periodontitis, are important factors which affect general and oral-health related quality of life in individuals with diabetes.

6.1.2 Impact of Periodontal Treatment on Glycaemic Control.

A number of randomised controlled trials (RCTs) have consistently demonstrated that treatment of periodontitis by non-surgical means is associated with a reduction of HbA1c levels in the short term. A Cochrane systematic review (Simpson et al., 2015) which included 35 studies of both type 1 and type 2 patients with diabetes (2,565 participants), reported a mean reduction of 0.29% in HbA1c 3-4 months following non-surgical therapy. Most included studies (83%) however were at high risk of bias and there was a clear lack of long-term studies. A recent update on this systematic review (Simpson et al., 2022) could not draw definitive conclusions on QoL (based on three studies), however weak evidence demonstrated some benefit following NST in periodontal patients with diabetes.

More recently, a 12-month RCT from our group (D'Aiuto et al., 2018), published a trial which included 264 participants with both moderate to severe periodontitis and type 2 diabetes. The impact of periodontal treatment (with a focus on reducing inflammation caused by periodontitis) on glycaemic control was investigated. The assigned treatments were intensive periodontal treatment (IPT) and control periodontal treatment (CPT). IPT included whole

mouth subgingival instrumentation and surgical therapy (if deemed necessary and appropriate) whilst CPT included only supra-gingival scaling and polishing at the same time points as IPT (after baseline and at 2, 6, 9 and 12 months (12M) after the completion of the first session of periodontal therapy). At 12M, after adjusting for a number of factors (e.g., baseline HbA1c, age sex, smoking status) the HbA1c was 0.6% (95% CI 0.3-0.9; p<0.0001) lower in the IPT group than in the CPT group. The reduction in HbA1c is higher than many of the RCTs published (Simpson et al., 2015, Simpson et al., 2022), however D'Aiuto et al. (2018) hypothesized that this might be in part due to the setting (university, specialist setting) and the clear focus on reduction of inflammation in the treatment of periodontitis, which included both non-surgical and surgical therapy (in many cases).

Therefore, although we have moderate-certainty evidence that periodontal therapeutic interventions (predominantly NST) can improve glycaemic control in people with diabetes (Simpson et al., 2022), we have no information on how treatment may impact on OHRQoL beyond the short term (3-months) in this group of patients. Thus, it would be a priority to evaluate the impact of periodontal treatment on OHRQoL, to inform stakeholders on the potential benefits (or harms) of periodontal treatment from the patient's point of view in the context of diabetes. A positive impact on OHRQoL could serve as a significant additional motivator for patients with diabetes to seek periodontal care.

6.2 Aim

The aim of this study was to assess the impact of periodontal treatment on oral health related quality of life (OHRQoL) in patients with type 2 diabetes over 12 months of follow-up.

The work in this chapter was an analysis of a secondary outcome of a randomised controlled trial (D'Aiuto et al., 2018).

6.3 Methods

6.3.1 Study Population and Setting

Participants were recruited from referrals to the Eastman Dental Hospital (Periodontology Unit), University College Hospital (Department of Endocrinology, outpatients), and Ealing and St Mary's Hospitals, London, UK. Additionally, patients were recruited from 15 general medical or dental practices in the Greater London area (identified using information from the Diabetes Research Network).

Inclusion Criteria

The study population included consecutive patients who:

- were aged over 18 years old
- were diagnosed with type 2 diabetes (for 6 months or longer) *
- were diagnosed with stage III/ IV periodontitis (Tonetti et al., 2018) with at least 20 periodontal pockets (periodontal probing depths of ≥4 mm and bleeding on probing)
- had a minimum of 15 teeth present

*The criteria for diagnosis of diabetes included a fasting plasma glucose of ≥7mmol/l (126mg/dl) or 2-hour plasma glucose ≥11.1mmol/l (200mg/dl) (World Health Organization and International Diabetes Foundation, 2006).

Exclusion Criteria

Participants were excluded from participating in the study if any of the following were identified:

- Uncontrolled systemic diseases (other than diabetes) e.g., cardiovascular disease (including hypertension), liver diseases, pulmonary diseases, end-stage renal failure or neoplasm;

- Hepatitis B or HIV infection
- Chronic treatment (>2 weeks) with drugs known to affect periodontal tissues e.g., cyclosporin or phenytoin
- Chronic systemic antibiotic treatment
- Pregnancy or breastfeeding

Approval was obtained from the joint University College London/ University College London Hospital Committees on Ethics of Human Research in November 2007 (Ref 07/H0714/97) and written consent was obtained for all eligible participants.

6.3.2 Outcome Measures

Primary Outcomes

The primary outcome measure was mean CS-OIDP score between the test (intensive periodontal therapy) and control groups at the 12-month follow-up.

Secondary Outcomes

- periodontal clinical parameters, including mean periodontal probing depth (PPD), recession (REC), clinical attachment level (CAL) and bleeding on probing (BOP) at 2-, 6- and 12M post therapy
- Change in responses at BL and 12M to single-item questions:
  - 'How would you rate the quality of your life?'
  - 'How is your general health?'
  - 'How is your periodontal health (i.e., health of your gums)?'
  - 'To what extend have the problems you have experienced affected your life overall and your quality of life?'

Correlations between mean PPD and CS-OIDP at BL and 12M, and change between time points.

6.3.3 Sample Size

This study presents the OHRQoL data of a RCT (D'Aiuto et al., 2018), designed and powered to compare the clinical effects of intensive periodontal therapy (non-surgical therapy and if required, surgical therapy) or no therapy (control group) in patients with severe periodontitis, on HbA1c at 12M.

A minimum sample of size of 129 participants per group was needed (assuming a 10% loss to follow-up) to detect a 1 percentage point (SD 2.1) between the two groups at 12M, with a 95% power at a 5% significance level.

Therefore, a post-hoc analysis was carried out to determine the power of the mean periodontal specific OIDP (CS-OIDP) presented in this chapter. This sample would have a 94% power to detect a difference between the test and control groups, assuming a minimally important difference of 5.5 in CS-OIDP between the two groups at a two-sided 5% significance level (common standard deviation of 7.0) (Tsakos et al., 2010).

6.3.4 Randomisation

A computer- generated table was used to randomly assign patients (1:1) to receive intensive periodontal treatment (IPT) or control periodontal treatment (CPT). Minimisation in allocation was included to account for diabetes duration, smoking status, sex and severity of periodontitis. Treatment group allocation was concealed using opaque envelopes and only revealed to the clinician and patient on the first day of treatment.

Dental staff delivering the intervention and performing the clinical examinations were not blinded to the participant's group allocation, however all other investigators (e.g., laboratory staff, vascular examiner and nurses collecting blood samples and anthropometric measures and report authors) were masked.

6.3.5 Study Operators and Procedures

Participants' treatment for diabetes was managed by the local endocrinology consultant and nurses (standard clinical guidelines) for both groups. All diabetes health-care providers were unaware of group assignment throughout the course of the study.

The periodontal therapy in both groups were carried out by two dental hygienists, two dentists, and three periodontists. Medical and dental histories were collected at baseline (BL), along with periodontal and clinical parameters at BL and at each study visit. This information was collected by two trained and calibrated examiners. A summary flowchart of the study design is shown in Figure 28.

All enrolled participants attended appointments for treatment; after BL, 2-, 6-, 9- and 12M after the completion of the first session of periodontal therapy. Following BL, teeth deemed to be severely compromised were extracted. Decisions on whether to extract included if the prognosis was very poor despite restorative efforts, severe bone loss (close to the root apex) or grade III mobility.

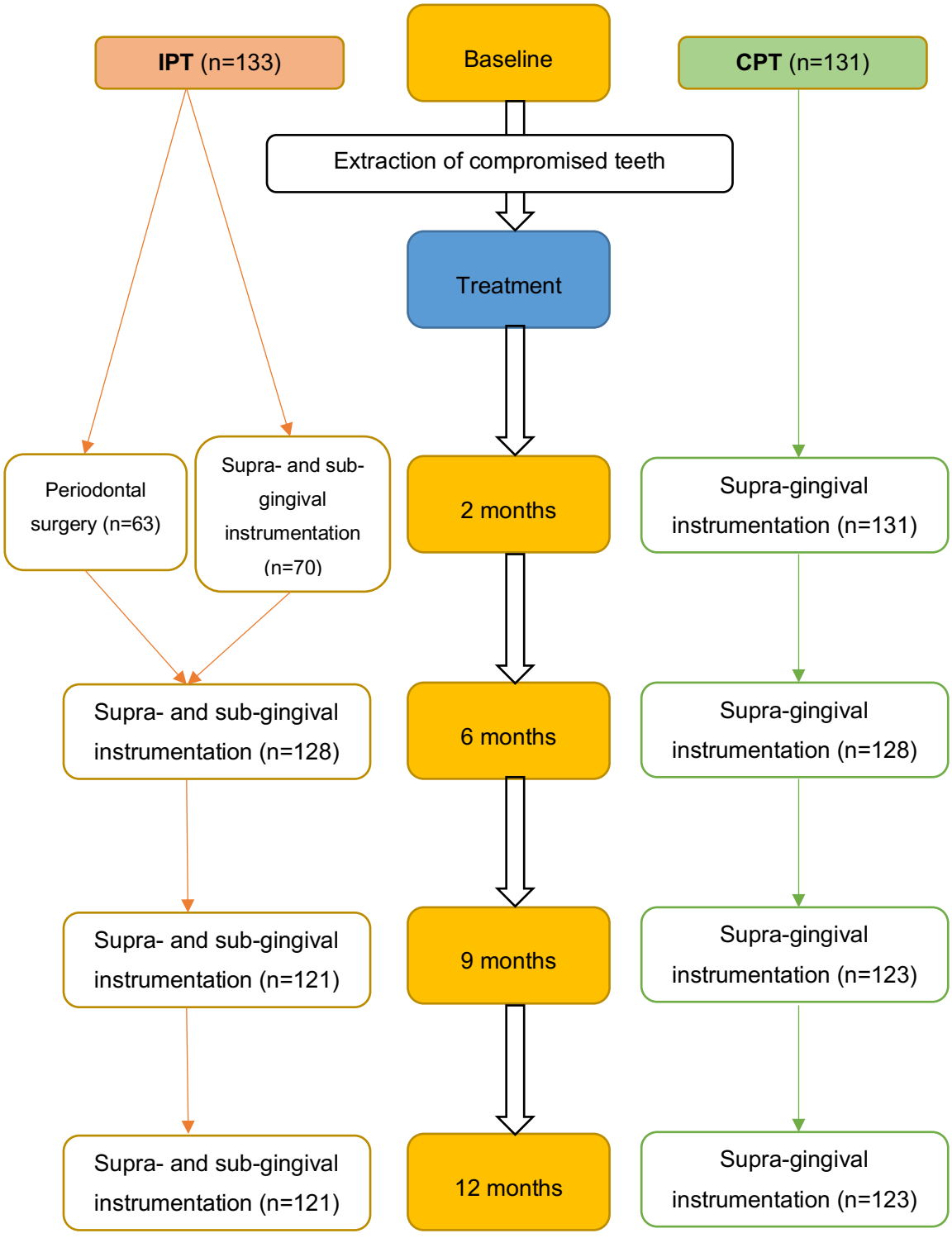


Figure 28. Flowchart of Study Design.

Intensive Periodontal Treatment (IPT) group

Participants in the IPT group (test) initially received a whole mouth, single, untimed session involving supra- and subgingival instrumentation under local anaesthesia. Two months following this, periodontal clinical assessment took place and those patients with good oral hygiene (full mouth plaque score of ≤20%) and at least one PPD ≥6 mm underwent periodontal surgery. Those patients with suboptimal oral hygiene and/or did not have residual PPD ≥6 mm, received additional subgingival instrumentation under local anaesthesia.

Subsequently, all patients in the IPT group received supra- and subgingival instrumentation under local anaesthesia every 3 months until completion of the study at 12M.

Control Periodontal Treatment (CPT) group

The CPT group (control) initially received a whole mouth, single, untimed session of supragingival scaling and polishing. Following this, participants received the same intervention (supragingival scaling and polishing) at identical time points as the test group (i.e., after BL, 2-, 6-, 9- and 12M after completion of the first session).

At the conclusion of the study, participants in the CPT group received additional periodontal therapy as needed.

6.3.6 Data Collection

Patient reported outcome measures

Oral health related quality of life was measured using the self-administered periodontal specific oral impacts on daily performance (CS-OIDP) questionnaire which was administered at BL and 12M following treatment. This validated measure, looked at 11 aspects of daily life (performances) such as eating, speaking, cleaning teeth, ability to carry out light physical activities, going out,

relaxing, sleeping, smiling, carrying out work/ role, emotional stability and social contact) and how oral conditions might impact these. If a respondent experienced an oral impact which was attributed specifically to a perceived periodontal reason (e.g. bad breath, mobile teeth), then he/she was asked to rate frequency of that impact according to a 5-point Likert scale as outlined below:

1. Less often than once a month
2. About 1-2 times a month
3. About 1-2 times a week
4. About 3-4 times a week
5. Every day or nearly every day

The severity of that impact was also scored using a 5-point Likert scale from 0-5, with 0 representing no effect and 5, a very severe effect.

At the same time points, participants were asked to rate their general health, periodontal health and QoL according to a global rating of change scale. The single-item questions according to a 5-point Likert scale (very poor, poor, fair, good or very good) for the following:

- Overall, would you say that your general health is…
- Overall, would you say that your periodontal health is…
- Considering your health, would you say that the overall quality of your life is…

Additionally, the following single-item questions at BL and 12M, according to a 6-point Likert scale (worsened a lot, worsened a little, stayed the same, improved a little, improved a lot and don't know) were administered:

- After finishing the treatment at the clinic, has your general health…
- After finishing the treatment at the clinic, has your periodontal health…
- After finishing the treatment at the clinic, has your quality of life…

Clinical outcomes

Fasting blood samples were collected at BL, 2, 6 and 12M after therapy and were centrifuged and stored (-70C) within 1 hour of collection for analysis at the termination of the study. Liquid chromatography was used to measure HbA1c and other outcomes of the study (e.g., lipid fractions, glucose, insulin).

At each appointment, in addition to the allocated treatment, periodontal parameters (six sites per tooth) were recorded. These included:

- Probing pocket depths
- Recession of the gingival margin relative to the cemento-enamel junction
- Presence or absence of supra-gingival dental plaque
- Bleeding on probing

Subsequently, mean whole mouth of periodontal lesions (PPD ≥4 mm) was calculated, relative percentages of presence of bleeding probing (full mouth BOP [number of sites with BOP / total number of sites in the mouth x 100]) and supra-gingival plaque score (full mouth plaque score [number of sites with visible plaque/ total number of sites in the mouth x 100]).

Any participant who showed progression of periodontitis, was exited from the study and the appropriate specialist care was administered.

6.3.7 Statistical Analysis

Descriptive statistics were performed with SPSS statistical software (IBM Corp. Released 2017. IBM SPSS Statistics for Macintosh, Version 25.0. Armonk, NY: IBM Corp.). Mean and standard deviations for quantitative data were used, unless otherwise indicated. The paired student *t* test was used to compare groups at BL and 12M, and changes within groups between the time points.

Analyses were conducted per protocol and the level of significance was taken to be $p < 0.05$.

Frequency distribution was calculated for single-item questions regarding periodontal health and general health and presented as proportions. Subsequently, the 5-point Likert scale for periodontal and general health at BL was dichotomised into, 'poor' (included categories of 'fair', 'poor' or 'very poor') or 'good' (included, 'good' or very good').

Patient Reported Outcome Measure Analysis (PROMs)

CS-OIDP

For each participant, a performance score was calculated for each of the 11 aspects of daily life. If a participant experienced an oral impact on a particular performance specifically attributed to their gums (e.g., bad breath or loose teeth), then the frequency was multiplied by the severity of the effect to obtain a performance score. If no oral impact was experienced, then a score of 0 was assigned. The CS-OIDP score was finally calculated by the addition of the 11 performances multiplied by 100, then divided by the maximum possible score (in this case, 275). Mean CS-OIDP scores (and standard deviation) were calculated for each treatment group. Frequency distribution of positive responses (i.e., a negative impact) were calculated for each group at BL and 12M and qualitatively described.

The change in CS-OIDP score was calculated by subtracting the score after treatment from the corresponding BL scores. Thus, positive scores indicated an improvement and negative scores, a deterioration in oral health-related quality of life. The paired student *t* test was used to compare BL and 12-month scores within each group.

The CS-OIDP scores were correlated with No. of PPD≥ 5mm, self-rated periodontal and general health, and quality of life using Spearman's rank

correlations (*p)*. Correlations were further interpreted according to Taylor (1990) where, if $p \leq 0.35$ the correlation was 'weak', 0.36-0.67 was 'moderate', 0.68-0.90 was 'strong' and ≥0.90 was 'very strong'. Each hypothesis test was two-sided and tested at the 0.05 significance level.

Minimally Important Difference

Minimally important difference (MID) for CS-OIDP scores from all participants were determined using the distribution-based approach (Tsakos et al., 2010). The standard error of measurement (SEM) was determined by multiplying the standard deviation of the mean CS-OIDP score at BL by the square root of one minus the reliability of the CS-OIDP (Tsakos et al., 2010, Masood et al., 2014). The value of the SEM was taken as the MID.

Effect size (η^2) was determined by subtracting the BL mean CS-OIDP from the 12M mean CS-OIDP, and dividing by the group standard deviation at BL. Interpretation of η^2 was according to Cohen (1988) whereby benchmark values were 0.2 (small), moderate (0.5) and large (0.8).

Global Ratings – Single-Item Questions

Single-item questions at BL and 12M were analysed as frequencies and percentages for each question (general health, periodontal health and QoL) by group and described qualitatively.

The Mann Whitney U test was used to determine if there were any statistically significant ($p<0.05$) differences in frequency distribution at BL and 12M between groups. A Wilcoxon signed rank test was used to detect differences within treatment groups ($p<0.05$).

Spearman's rank correlation coefficient was used to find the relationship between HbA1c, CS-OIDP, PPD≥5 mm, periodontal health and general health at BL and 12M. The 2-tailed significance level was set a $p<0.05$.

6.4 Results

264 patients (165 male and 99 female) were recruited for this study between 1st July 2007 and 1st of January 2015. A summary of BL characteristics of the intention to treat population are shown in Table 26. Full characteristics were previously described (D'Aiuto et al., 2018). No statistically significant differences in BL characteristics, other than age (p=0.04), between the IPT and CPT groups were found.

Table 26. Baseline Socio-Demographics

	Intensive Periodontal Therapy (IPT)	**Control Periodontal Therapy (CPT)**
n	133	131
Mean Age (± SD)	58.2 (± 9.7)	55.5 (± 10.0)
Gender, n (%)		
Male	82 (62)	83 (63)
Female	51 (38)	48 (37)
Ethnicity, n (%)		
White	43 (32)	52 (40)
Asian	54 (41)	43 (33)
African	25 (19)	34 (26)
Other	11 (8)	2 (2)
Smoking history, n (%)		
Never	75 (56)	70 (53)
Current	18 (14)	19 (15)
Former	40 (30)	42 (32)

Overall, the two groups appeared well balanced in terms of chief demographic characteristics. The mean age of participants in the IPT and CPT groups were 58.2 (± 9.7) years and 55.5 (± 10.0) years, respectively. The mean difference in age (2.7 ±1.3, 95% CI 0.17 – 5.2) between the two groups was found to be statistically significant (p=0.04). The majority (41%) of participants in the IPT group were of Asian ethnicity (n=54), whilst in the CPT group, most (40%) were of White ethnicity (n=52). In both groups, the majority were never smokers, 56% (n=75) in the IPT group and 53% (n=70) in the CPT group.

The IPT group included 133 patients at BL. Following the initial supra- and subgingival instrumentation under local anaesthesia, 63 participants (47.3%) underwent periodontal surgery and 70 (52.6%) had further subgingival instrumentation alone. 121 patients from the IPT group completed the study (five participants were lost to follow-up at 2 months, and seven participants were lost at 6 months).

The CPT group initially included 131 participants. 123 participants presented at the 12-month follow up and 8 discontinued treatment (three participants were lost to follow up at 2 months, whilst five were lost to follow-up at 6 months).

6.4.1 Patient Reported Outcome Measures (PROMs)

CS-OIDP

The questionnaire used in this trial was specifically tailored to record impacts attributable to periodontitis alone, therefore the condition specific OIDP was calculated (rather than the generic OIDP).

Overall, there appeared to be few differences in mean CS-OIDP when comparing groups at BL and 12M. Change of scores from BL to 12M within each group, however, were statistically significant for both groups. At BL, the mean CS-OIDP score for the IPT group (n=132) was 10.1 (±15.9) and for the CPT group (n=130) was 12.1 (±19.7). The difference between groups was not

statistically significant (p=0.36). At 12M the mean score was 5.2 (± 11.5) for IPT (n=132) and 7.3 (±13.8) for CPT (n=130) which again was not found to be significantly different (p=0.18) between groups. The change in scores from BL to 12M between groups was not found to be significantly different (p=0.96). The within group change in mean CS-OIDP (both groups improved) was statistically significant for both the IPT group (4.81, p<0.001) and CPT group (4.55, p=0.006).

Generally, there was a trend for improvement with respect to individual performances between BL and 12M for both groups. Figure 29. displays the proportion of respondents who recorded a negative impact in a performance at BL and 12M in the CPT group. At BL (n=130), almost half of the participants reported a negative impact with eating (n=57, 43.8%), whilst 39.2% (n=51) experienced difficulty with cleaning their teeth. Approximately one third of participants in this group felt it was difficult to relax (n=44, 33.8%) and/or smile (n=43, 33.1%), whilst difficulty with emotional state (n=36, 27.7%), enjoying contact with others (n=31, 23.8%) and challenges with sleeping (n=36, 27.7%) were also frequently reported impacts. At 12M post-treatment (n=121), the proportion of respondents indicating a negative impact was less for all categories. Difficulty eating remained the most prevalent aspect of daily life affected (n=46, 38.0%), whilst difficulty with smiling (n=34, 28.1%), cleaning teeth (n=32 , 26.4%) and relaxing (n=28 , 23.1%) were also commonly reported. The largest proportional reduction (12.8%) between BL and 12M was for the reported difficulty with cleaning teeth, followed by ability to relax (10.7%).

In the IPT group, there was a reduction in the proportion of respondents who reported negative impacts (for every performance) between BL and 12M (Figure 30). At BL (n=132), the greatest proportion of respondents who reported an impact was in difficulty cleaning teeth (n=61, 46.2%), followed by difficulty with eating (n=59, 44.7%). Almost one third of respondents reported a negative impact with smiling (n=40, 30.3%) and ability to enjoy contact with others (n=40, 30.3%) and 25% (n=33) reported difficulty with managing their emotional state.

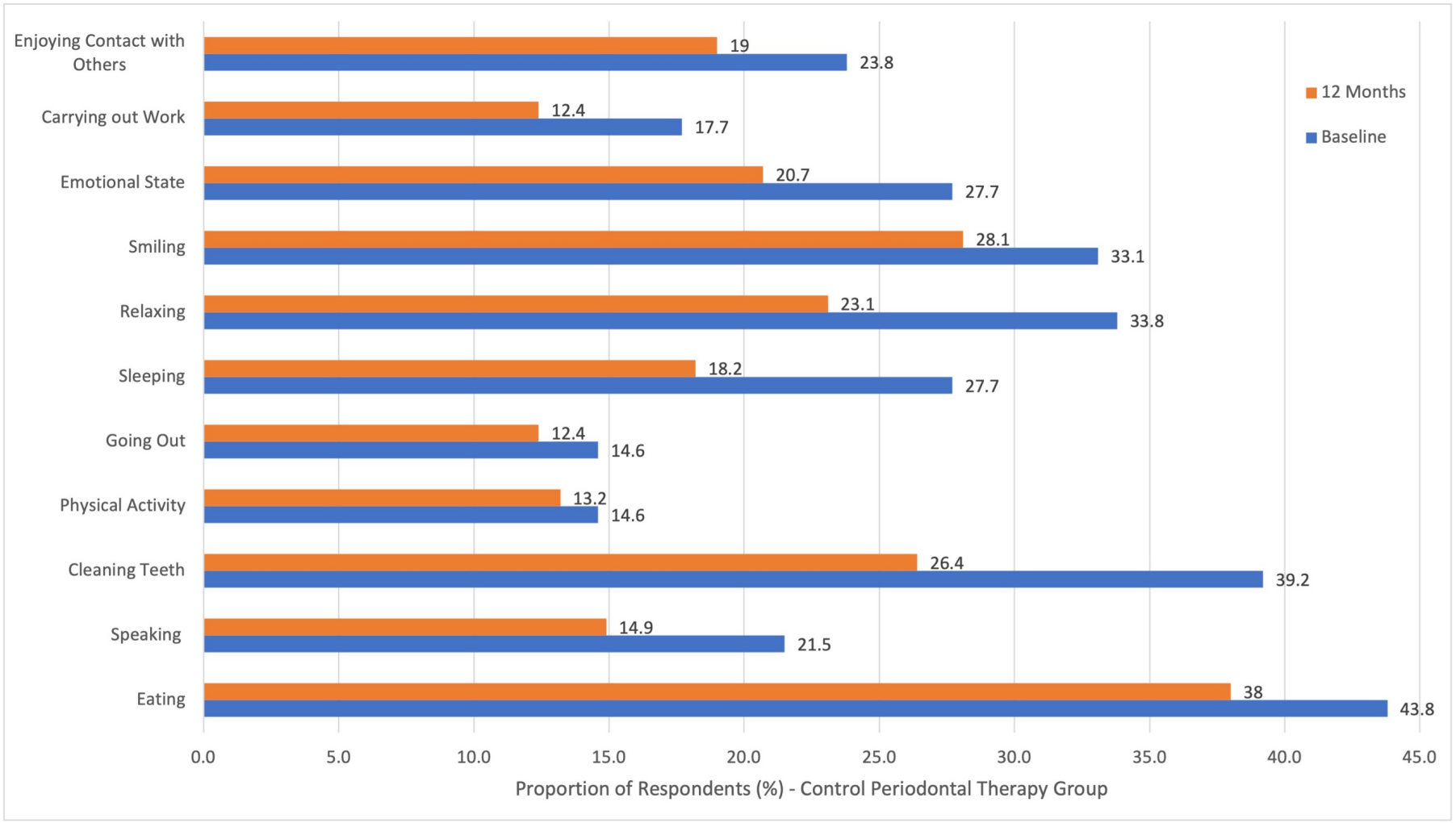


Figure 29. Recorded impacts (CS-OIDP) of participants in the CPT group at baseline (n=130) and 12 months (n=121).

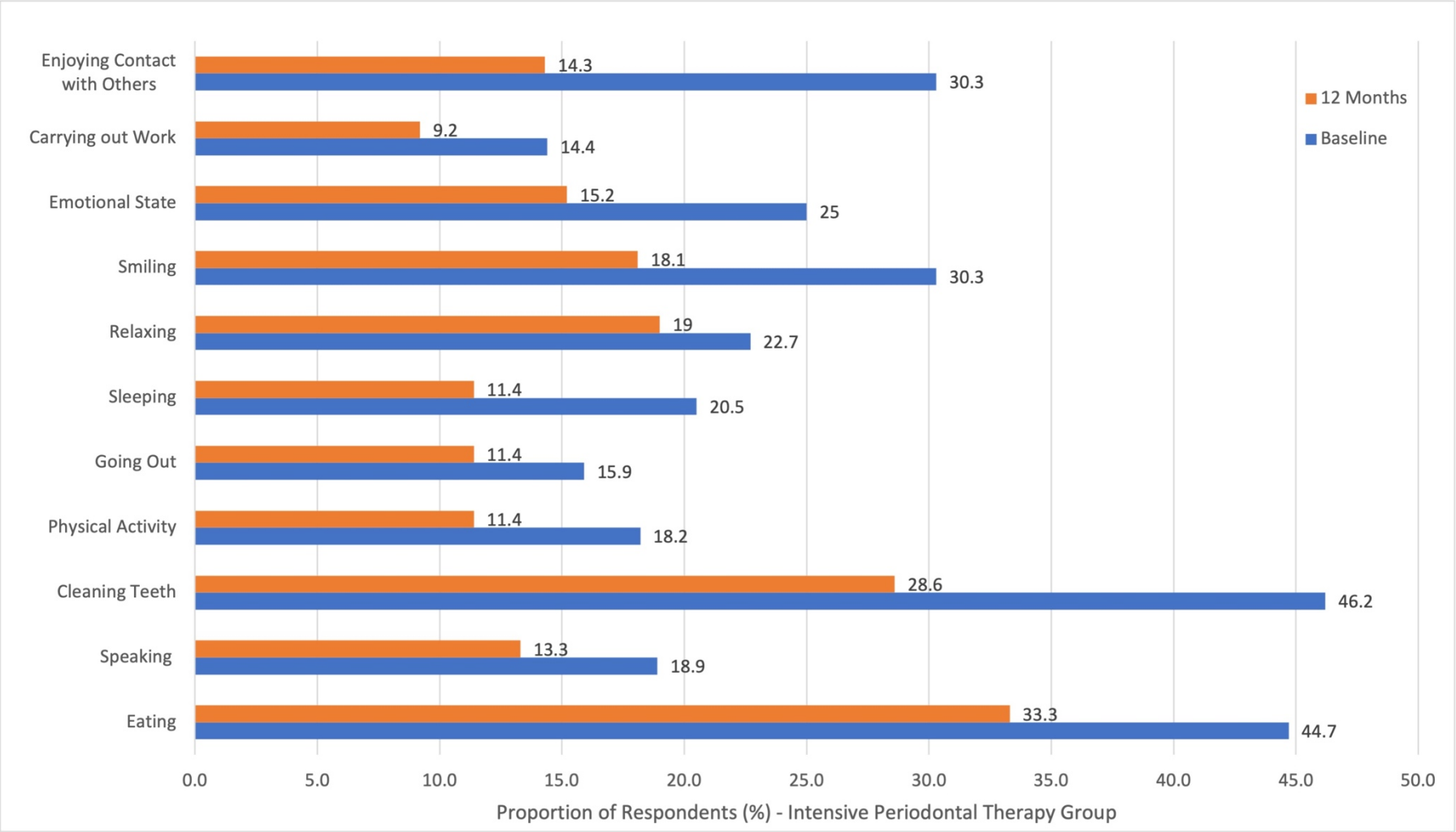


Figure 30. Recorded impacts (CS-OIDP) of participants in the IPT Group at baseline (n=132) and 12 months (105).

At 12M (n=105), difficulty with eating was the most frequently reported impact (n=35, 33.3%), followed by difficulty with cleaning teeth (n=30, 28.6%), whilst difficulty with relaxing (n=20, 19%) and smiling (n=19, 18.1%) were also frequently impacted. The greatest reduction in the proportion of respondents reporting a negative impact between BL and 12M was for difficulty with cleaning teeth (17.6%), closely followed by ability to enjoy contact with others (16%) and difficulty with smiling (12.2%).

Single-Item Questions

General Health

General health was rated at BL and 12M post treatment. The proportions according to treatment group, are displayed in Table 27. At BL, the majority of participants, 43% (n=43) in the IPT group, rated their general health as, 'fair', with a similar proportion, 43.1% (n=44), in the CPT group. Very few participants rated their health as, 'very poor' (IPT=3, CPT=2), which was similar for the 'very good' category (IPT=1, CPT=4). No statistically significant difference was detected (p=0.96) between the groups.

Table 27. Responses to single-item question rating general health at baseline and 12 months.

General Health	Intensive Periodontal Therapy (IPT)		Control Periodontal Therapy (CPT)	
	BL (n=100)	12M (102)	BL (n=102)	12M (n=108)
Very Poor % (n)	3% (3)	5.9% (6)	2% (2)	1.9% (2)
Poor % (n)	19% (19)	12.7% (13)	20.6% (21)	14.8% (16)
Fair % (n)	43% (43)	35.3% (36)	43.1% (44)	41.7% (45)
Good % (n)	34% (34)	42.2% (43)	30.4% (31)	37% (40)
Very Good % (n)	1% (1)	3.9% (4)	3.9% (4)	4.6% (5)

BL=baseline, 12M= 12 months

At 12M, 42.2% (n=43) of the participants in the IPT group rated their general health as, 'good', compared with 37% (n=40) in the CPT group. The greatest number of participants (n=45, 41.7%) in the CPT group rated their general health as, 'fair' at 12M. The difference between the groups was not found to be significant (p=0.85). The within group difference for self-rated general health between BL and 12M for the IPT group was not found to be statistically significant (p=0.07), nor was the within group difference for the CPT group (0.12).

Periodontal Health

Participants rated their periodontal health at BL and 12M according to a 5-point Likert scale with results displayed in Table 28. Self-rated periodontal health improved in both groups between BL and 12M. There were 88 responses in the IPT group and 73 in the CPT group at BL. The greatest proportion of participants in both groups rated their periodontal health at BL as, 'poor', which was 45.5% (n=40) in the IPT group and 53.4% (n=39) in the CPT group. Almost one third (33.0%, n=29) rated their periodontal health as, 'fair', in the IPT group, whilst this was 21.9% (n=16) in the CPT group. No statistically significant difference was detected (p=0.82) between the groups.

At 12M, self-rated periodontal health appeared to improve in both groups. In the IPT group, most respondents (45%, n=45) reported their periodontal health was, 'fair' or, 'good' (35%, n=35). 10% (n=10) rated their periodontal health as, 'very good', whereas at BL, no participants chose this response. The CPT group at 12M reported the highest proportion in the 'good' category (42.1%, n=45), whilst 33.6% (n=36) self-rated their periodontal health is, 'fair'. 5.6% (n=6) felt their periodontal health was, 'very good', which slightly improved from BL (2.7%, n=2). There was no statistically significant difference detected between the groups (p=0.54). Within group comparison between BL and 12M showed a highly significant difference (improvement) in periodontal health for both the IPT ($p<0.001$) and CPT ($p<0.001$) groups.

Table 28. Responses to single-item question rating periodontal health at BL and 12M.

Periodontal Health	**Intensive Periodontal Therapy (IPT)**		**Control Periodontal Therapy (CPT)**	
	BL (n=88)	12M (100)	BL (n=73)	12M (n=107)
Very Poor % (n)	14.8% (13)	2% (2)	11.0% (8)	3.7% (4)
Poor % (n)	45.5% (40)	8% (8)	53.4% (39)	15% (16)
Fair % (n)	33.0% (29)	45% (45)	21.9% (16)	33.6% (36)
Good % (n)	6.8% (6)	35% (35)	11.0% (8)	42.1% (45)
Very Good % (n)	0.0% (0)	10% (10)	2.7% (2)	5.6% (6)

BL=baseline, 12M= 12 months

Quality of Life

Participants were asked to rate their overall QoL at BL and 12M with the distribution of responses displayed in Table 29. At BL, there were 91 responses in the IPT group and 82 in the CPT group. In both groups, most participants rated their QoL as, 'good' with more than half in the IPT group

(50.5%, n=46) and 45.1% (n=37) in the CPT group. Those who rated their QoL as, 'fair' were 37.4% (n=34) and 39.0% (n=32) in the IPT and CPT groups respectively. There was no statistically significant difference between the groups at BL (p=0.69).

Table 29. Responses to single-item question rating quality of life at BL and 12M.

Quality of Life	**Intensive Periodontal Therapy (IPT)**		**Control Periodontal Therapy (CPT)**	
	BL (n=91)	12M (n=102)	BL (n=82)	12M (n=106)
Very Poor % (n)	0.0% (0)	1.0% (1)	1.2% (1)	1.9% (2)
Poor % (n)	8.8% (8)	8.8% (9)	6.1% (5)	7.5% (8)
Fair % (n)	37.4% (34)	25.5% (26)	39.0% (32)	28.3% (30)
Good % (n)	50.5% (46)	58.8% (60)	45.1% (37)	49.1% (52)
Very Good % (n)	3.3% (3)	5.9% (6)	8.5% (7)	13.2% (14)

BL=baseline, 12M= 12 months

At 12M post therapy, still, the majority of participants in both groups rated their QoL as, 'good' (IPT; 58.8%, n=60) and CPT; 49.1%, n=52), whilst, 'fair' was once again the second most popular rating (IPT; 25.5%, n=26 and CPT; 28.3%, n=30). A greater proportion of participants rated their QoL as, 'very good' at 12M, with 5.9% (n=6) in the IPT group compared with 3.3% (n=3) at BL, and 13.2% (n=14) in the CPT group, compared with 8.5% (n=7) at BL. No statistically significant difference was found between the groups at 12M (p=0.71). The within group change from BL to 12M was statistically significant for the CPT group (p=0.002) but not for the IPT group (p=0.23).

General Health – Post Treatment

At the 12M follow-up visit, participants were asked to rate how their general health had changed, with distribution of responses are shown in Figure 31. In general, the majority of participants felt their general health had improved in comparison to BL. In the IPT group, 103 participants results were recorded and 110 in the CPT group. No participants felt that their general health had worsened a lot. Almost half (47.27%, n=52) of the CPT group felt that their general health had improved a little, compared with 33.98% (n=35) of the IPT group. 37.86% (n=39) of the IPT group felt that their general health had improved, whilst 22.73% (n=25) of the CPT group felt the same. A small proportion from both groups (IPT: 3.88%, n=4, CPT: 2.73%, n=3) felt their general health had worsened a little over the 12 months of follow up. No statistically significant difference between the groups was detected (p=0.07).

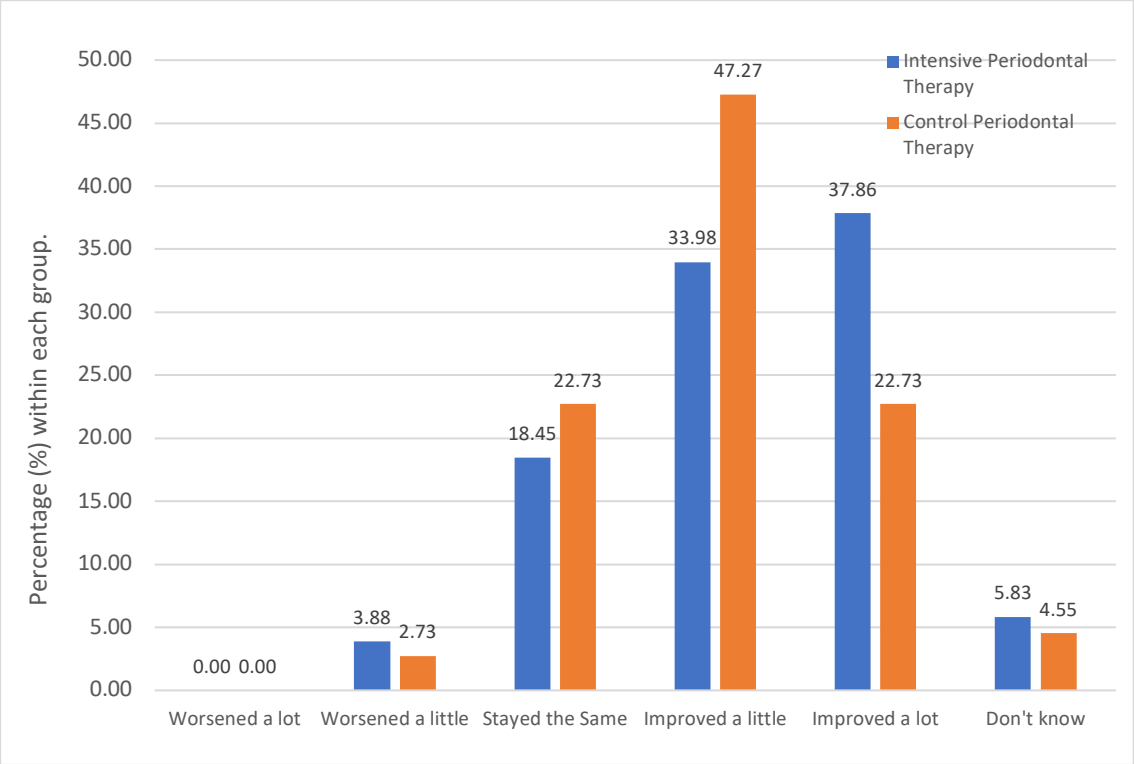


Figure 31. Distribution of responses at 12M post treatment regarding general health.

Periodontal Health – Post Treatment

Overall, the majority of participants in both groups felt that their periodontal health improved following treatment, despite the intervention. Periodontal health at 12M post-treatment was rated by 103 patients in the IPT group and 109 in the CPT group. The results are depicted in Figure 32. In the IPT group, 52.43% (n=54) of respondents felt their periodontal condition had improved a lot 12M following therapy, compared with 35.78% (n=39) in the CPT group. Participants in the CPT group felt their periodontal condition had improved to a lesser extent, with 44.04% (n=48) feeling that their periodontal health improved a little (compared with 35.92%, n=37 for the IPT group). Very few respondents

felt that their periodontal health had worsened a little or a lot. A statistically significant difference was detected between the groups (p=0.04).

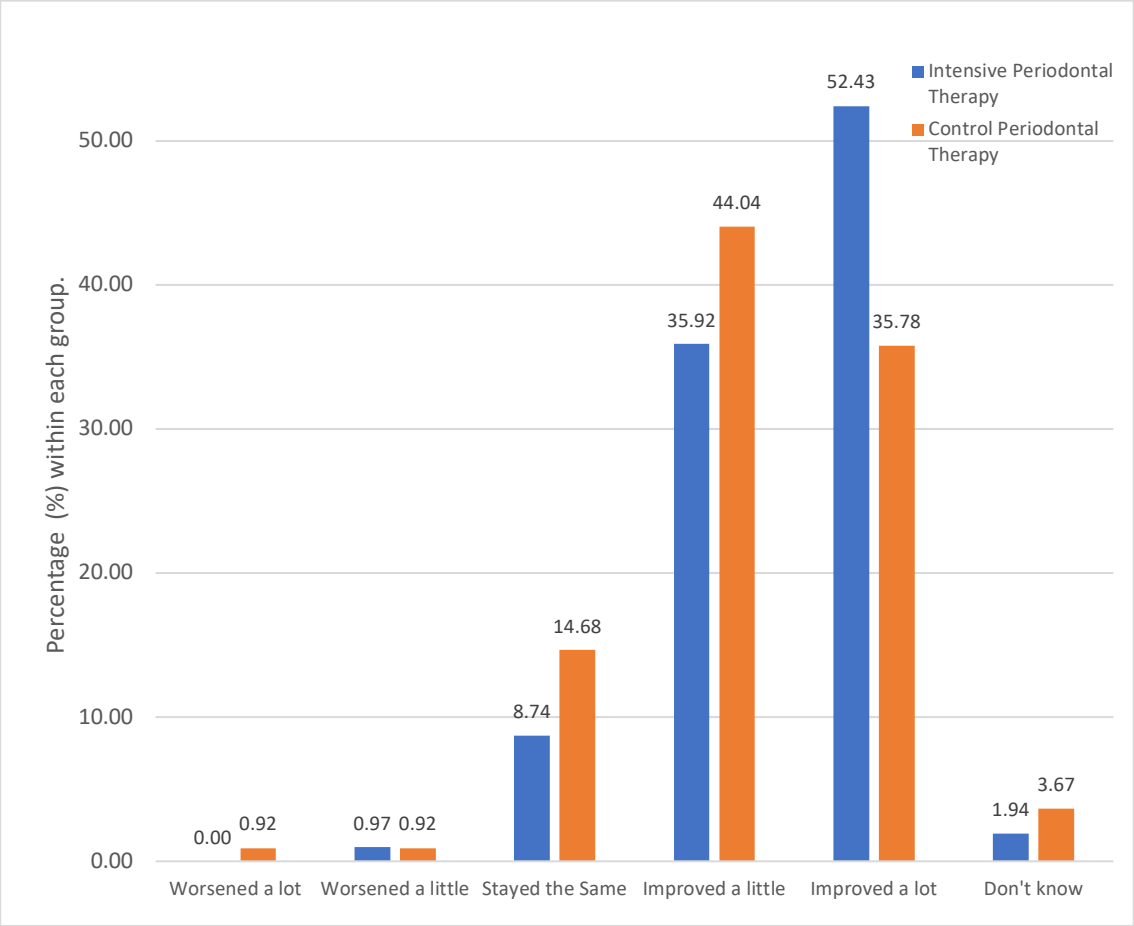


Figure 32. Distribution of responses at 12M post treatment regarding to periodontal health.

6.4.2 Clinical Outcomes

Baseline clinical characteristics of both groups are summarised in Table 30. Overall, baseline characteristics were similar between groups with no statistically significant differences. The mean number of teeth in both groups were the same, 26 (±4) teeth, and mean No. of PPD≥ 5mm (relating to extent of

disease) was similar with 55 (±27) in the IPT group, and 50 (±22) in the CPT group. Additionally, both groups displayed the same level of diabetic control with HbA1c of 8.1 (±1.7)%.

Table 30. Baseline clinical characteristics of population (summarised from D'Aiuto et al., 2018).

	Intensive Periodontal Therapy (IPT)	**Control Periodontal Therapy (CPT)**
n	133	131
Number of teeth (± SD)	26 (± 4)	26 (± 4)
Full mouth plaque score (%) (± SD)	74 (± 19)	74 (± 19)
Full mouth bleeding score (%) (± SD)	65 (± 21)	64 (± 19)
Periodontal probing depth (mm) (± SD)	3.9 (± 087)	3.9 (± 0.7)
Number of pockets ≥5 mm (± SD)	55 (± 27)	50 (± 22)
Percentage of pockets ≥5 mm (± SD)	34 (± 16)	35 (± 16)
HbA1c (%) (± SD)	8.1 (± 1.7)	8.1 (± 1.7)

All values are given as means (standard deviations)

Overall, there were improvements in all clinical improvements for both groups (Table 31) which were highly significant, although the magnitude of improvement was consistently greater for the IPT versus the CPT group. There was statistically significant ($p<0.001$) reduction in the No. of PPD≥ 5mm from

BL (54.6 ±27.3) to 12M (12.0 ±14.8) in the IPT group (mean reduction 42.6 ±22.3). The CPT group displayed a more modest mean reduction in the No. of PPD≥ 5mm of 10.9 (±18.3) and this was also highly significant ($p<0.001$).

Mean PPD statistically significantly ($p<0.001$) reduced in the IPT group from 3.9 (±0.8) mm at BL, to 2.8 (±0.7) mm at 12M. The CPT group also experienced a reduction in PPD from 3.9 (±0.7) mm at BL to 3.6 (±0.9) mm at 12M. This was also statistically significant ($p<0.001$).

Full mouth plaque and bleeding scores significantly reduced between BL and 12M for both groups, although a greater magnitude of reduction was noted for the IPT group in both parameters. The FMPS was 74 (±18) % for the IPT group which reduced 39.2 (±20.5) % at 12M. The mean reduction in FMPS was 34.9 (±22.1) % which was highly significant ($p<0.001$). The CPT group showed a similarly highly significant ($p<0.001$) reduction in FMPS from 74.0 (±18.5) % at BL to 60.2 (±21.0) % at 12M (mean reduction of 13.9±20.6)%. FMBS in the IPT group showed a mean of 64.8 (±20.5) % at BL and this reduced to 30.4 (±17.1) % at 12M. This reduction (34.4 ±19.8%) was statistically significant ($p<0.001$). The CPT group experienced a smaller statistically significant ($p<0.001$) mean reduction (7.5 ±17.1%) between BL (64.1 ±18.9%) and 12M (56.6 ±20.2%).

HbA1c in both groups were 8.1(± 1.7) % at BL. At the 12M follow up, The IPT group exhibited an HbA1c of 7.8 (±0.2)% ($p=0.04$), whilst the CPT group showed a mean of 8.3 (±0.2)% ($p=0.18$). The between group comparison at 12M showed a statistically significant difference ($p=0.03$) in the change (0.6%, 95% CI 0.1-1.0) with a p-value of 0.01.

Table 31. Change in clinical outcomes between baseline and 12 months.

	Intensive Periodontal Therapy (IPT)				Control Periodontal Therapy (CPT)			
	BL	12M	Δ	*p*	BL	12M	Δ	*p*
No. of PPD ≥5 mm (±SD)	54.6 (±27.3)	12.0 (±14.8)	42.6 (±22.3)	<0.001*	50.2 (±21.7)	39.3 (±25.0)	10.9 (±18.3)	<0.001*
PPD mm (±SD)	3.9 (±0.8)	2.8 (±0.7)	1.2 (±0.7)	<0.001*	3.9 (±0.7)	3.6 (±0.9)	0.3 (±0.6)	<0.001*
FMPS % (±SD)	74.1 (±18.8)	39.2 (±20.5)	34.9 (±22.1)	<0.001*	74.0 (±18.5)	60.2 (±21.0)	13.9 (±20.6)	<0.001*
FMBS % (±SD)	64.8 (±20.5)	30.4 (±17.1)	34.4 (±19.8)	<0.001*	64.1 (±18.9)	56.6 (±20.2)	7.5 (±17.1)	<0.001*
HbA1c % (±SD)	8.1 (±1.7)	7.8 (±0.2)	-0.3 (±1.1)	0.04*	8.1 (±1.7)	8.3 (±0.2)	0.2 (±1.2)	0.18

*statistically significant (p<0.05). *p* value – change within group between BL and 12M.
BL=baseline, 12M= 12 months, Δ=change from BL to 12M, *p*=p-value, CS-CS-OIDP=Condition Specific Oral Impacts on Daily Performance, SD=standard deviation, FMPS=full mouth plaque score, FMBS=Full mouth bleeding score, PPD=periodontal probing depths, mm=millimetres, HbA1c=glycosylated haemoglobin

Correlations

Spearman's rank correlations by treatment group, were calculated at BL (Table 33), 12M (Table 34) and for the change in values between BL and 12M (Table 35).

Intensive Periodontal Therapy Group

In the IPT group at BL (n=133), there was a statistically significant moderate negative correlation between CS-OIDP score and periodontal health (*p*= -0.44, p<0.001) and a weak negative correlation with QoL (*p*= -0.26, p=0.02). This negative coefficient meant that having a worse self-rated periodontal health/ quality of life (lower score) correlated with a worse OHRQoL (higher score). Periodontal health and quality of life displayed weak positive statistically significant correlation (*p*=0.31, p=0.004). No other statistically significant correlations were found at this time point.

At 12M in the IPT group (n=121), there were weak negative statistically significant correlations found between CS-OIDP and periodontal health (*p*= -0.20, p=0.05), general health (*p*= -0.27, p=0.006) and QoL (*p*= -0.21, p=0.04). Additionally, moderate positive correlations were found between periodontal health and general health (*p*=0.46, p<0.001) and QoL (*p*=0.36, p<0.001), and between general health and QoL (*p*=0.60, p<0.001). With regard to change in scores between BL and 12M, a moderate positive correlation was found between No. of PPD≥ 5mm and FMBS (*p*=0.42, p<0.001). No other statistically significant correlations were observed at this time point.

Control Periodontal Therapy Group

In the CPT group at BL (n=131), a weak negative statistically significant correlation was found between CS-OIDP and periodontal health (*p*= -0.28, p=0.02) and a moderate correlation with QoL (*p*= -0.37, p<0.001). Periodontal health also had a statistically significant weak positive correlation with QoL (*p*= 0.28, p=0.02). No other statistically significant correlations were found at this time point.

More statistically significant correlations were found at 12M (n=123), which included a weak negative correlation between CS-OIDP and general health (*p*= -0.28, p=0.003) and a moderate correlation with QoL (*p*= -0.45, p<0.001). Periodontal health was moderately correlated with both general health (*p*= 0.47, p<0.001) and QoL (*p*= 0.37, p<0.001). QoL was moderately correlated with general health (*p*= 0.67, p<0.001) and had a weak negative correlation with No. of PPD≥ 5mm (*p*= -0.19, p=0.05). Similar to the IPT group, the change in No. of PPD≥ 5mm and FMBS between BL and 12M displayed a moderate positive correlation (*p*= 0.40, p<0.001). No other statistically significant correlations were observed at this time point.

Minimally Important Difference

Table 32 displays the estimation of MID using the distribution approach, which was 5.32 for CS-OIDP, with a small to moderate effect size (Cohen, 1988) of 0.29 observed. 30.74% (n=74) of participants experienced a change in CS-OIDP greater than or equal to the MID, which was made up of 36 participants from the CPT group and 38 from the IPT group.

Table 32. Condition Specific Oral Impacts on Daily Performances for the whole sample (n=264): score changes over time and minimally important difference.

Condition Specific Oral Impacts on Daily Performance	
Mean score at baseline (SD)	11.03 (18.03)
Mean score at 12 months (SD)	5.82 (12.28)
Change (95% CI)	5.21 (3.16 – 7.25)
p value within group	p <0.001
Minimally Important Difference (MID)	
Effect size	0.29
Standard Error of Measurement	5.32

Table 33. Spearman's rank correlations at baseline.

BASELINE		CS-OIDP	No. of PPD≥ 5mm	Periodontal Health	General Health	QoL
IPT Group (n=133)	CS-OIDP	1 (0)	0.12 (0.18)	**-0.44 (<0.001)***	-0.13 (0.20)	**-0.26 (0.02)***
	No. of PPD≥ 5mm		1 (0)	-0.10 (0.36)	-0.04 (0.71)	-0.13 (0.21)
	Periodontal Health			1 (0)	-0.03 (0.82)	**0.31 (0.004)***
	General Health				1 (0)	-0.02 (0.90)
	QoL					1 (0)
CPT Group (n=131)	CS-OIDP	1 (0)	0.08 (0.39)	**-0.28 (0.02)***	0.09 (0.10)	**-0.37 (<0.001)***
	No. of PPD≥ 5mm		1 (0)	-0.19 (0.10)	-0.02 (0.83)	0.07 (0.54)
	Periodontal Health			1 (0)	-0.003 (0.99)	**0.28 (0.02)***
	General Health				1 (0)	0.24 (0.06)
	QoL					1 (0)

All data given as: Spearman's rank correlation coefficient (p-value) *: statistically significant ($p<0.05$) IPT: Intensive Periodontal Therapy Group, CPT: Control Periodontal therapy Group, CS-OIDP: condition specific Oral Impacts on Daily Performance, No. of PPD≥ 5mm: mean number of periodontal probing depths greater than or equal to 5 millimetres (posterior sextants), QoL: Quality of life

Table 34. Spearman's rank correlations at 12 months post-treatment.

12 MONTHS		CS-OIDP	No. of PPD≥ 5mm	Periodontal Health	General Health	QoL
IPT Group (n=121)	CS-OIDP	1(0)	0.11 (0.25)	**-0.20 (0.05)***	**-0.27 (0.006)***	**-0.21 (0.04)***
	No. of PPD≥ 5mm		1 (0)	-0.05 (0.66)	0.02 (0.84)	-0.04 (0.70)
	Periodontal Health			1 (0)	**0.46 (<0.001)***	**0.36 (<0.001)***
	General Health				1 (0)	**0.60 (<0.001)***
	QoL					1 (0)
CPT Group (n=123)	CS-OIDP	1 (0)	0.04 (0.67)	-0.10 (0.31)	**-0.28 (0.003)***	**-0.45 (<0.001)***
	No. of PPD≥ 5mm		1 (0)	-0.06 (0.57)	-0.04 (0.70)	**-0.19 (0.05)***
	Periodontal Health			1 (0)	**0.47 (<0.001)***	**0.37 (<0.001)***
	General Health				1 (0)	**0.67 (<0.001)***
	QoL					1 (0)

All data given as Spearman's rank correlation coefficient (p-value).*: statistically significant (p,0.05). IPT: Intensive Periodontal Therapy Group, CPT: Control Periodontal therapy Group, CS-OIDP: condition specific Oral Impacts on Daily Performance, No. of PPD≥ 5mm: mean number of periodontal probing depths greater than or equal to 5 millimetres (posterior sextants), QoL: Quality of Life

Table 35. Spearman's rank correlations of change in scores between baseline and 12 months.

SCORE CHANGE		Δ CS-OIDP	Δ No. of PPD≥ 5mm	Δ HbA1c (%)	Δ FMBS (%)
IPT Group	Δ CS-OIDP	1 (0)	-0.04 (0.64)	-0.03 (0.70)	0.03 (0.73)
	Δ No. of PPD≥ 5mm		1 (0)	-0.01 (0.90)	**0.42 (<0.001)***
	Δ HbA1c (%)			1 (0)	-0.07 (0.45)
	Δ FMBS (%)				1 (0)
CPT Group	Δ CS-OIDP	1 (0)	0.07 (0.43)	0.08 (0.38)	-0.002 (0.98)
	Δ No. of PPD≥ 5mm		1 (0)	-0.7 (0.43)	**0.40 (<0.001)***
	Δ HbA1c (%)			1 (0)	-0.06 (0.55)
	Δ FMBS (%)				1 (0)

All data given as: Spearman's rank correlation coefficient (p-value). *: statistically significant ($p<0.05$), Δ: change in score/ value between baseline and 12 months.
IPT: Intensive Periodontal Therapy Group, CPT: Control Periodontal therapy Group, CS-OIDP: condition specific Oral Impacts on Daily Performance, No. of PPD≥ 5mm: mean number of periodontal probing depths greater than or equal to 5 millimetres (posterior sextants), FMBS: full mouth bleeding score.

6.5 Discussion

6.5.1 Key Findings

Treatment of periodontitis improves OHRQoL (CS-OIDP) and self-rated periodontal health significantly, regardless of intensity of periodontal therapy in patients with diabetes. Prior to treatment, the proportion of patients reporting a negative impact was the greatest for; i) difficulty with eating and ii) difficulty in cleaning teeth (similar for both groups). For both groups, at 12M, difficulty with cleaning teeth showed the largest reduction in the proportion of respondents indicating this as being negatively impacted (IPT:17.6%, CPT: 12.8% reduction). A minimally important difference of 5.32 (η^2 =0.29) was calculated for CS-OIDP using the distribution-based approach.

Improvement in metabolic control (HbA1c) was not significantly correlated with OHRQoL for either treatment approach, however there was a weak correlation (r= 0.17, p=0.007) with improved diabetic control and an improvement in extent of periodontitis (number of PPD≥5 mm).

Self-rated periodontal health correlated with self-rated QoL at BL and 12M regardless of the treatment approach, in patients living with diabetes.

6.5.2 Agreements and Disagreements with Other Studies

There is limited evidence of the impact of periodontal therapy on OHRQoL in patients with diabetes. A recently updated Cochrane systematic review found that only three studies included measures for QoL (Simpson et al., 2022), and the studies were found to be 'sparse and mixed', however there appeared to be some benefit from periodontal therapy on QoL in relation to patients living with diabetes.

It is unclear how the impact of periodontal therapy on OHRQoL might be affected by diabetes, however my study demonstrates that OHRQoL improves

significantly following periodontal therapy in this group of patients despite the modality of treatment. In contrast to the present study, the majority of studies published to date have 3-6 months follow-up. One short term randomised controlled trial of 91 participants (Vergnes et al., 2018) found that following non-surgical therapy, OHRQoL improved, however QoL showed no statistically significant change. Additionally, in contrast to the present study, no statistically significant change was found before and after therapy in HbA1c levels. The contrast in results may be in part due to the differing treatment modality (NST alone, whereas the current study included both NST and ST), lower baseline HbA1c levels (7.8% versus 8,1% in the present study), small sample size (n=91), and/or the short follow-up time.

Strong evidence exists to demonstrate that periodontal therapy improves OHRQoL in patients with periodontitis (Shanbhag et al., 2012, Botelho et al., 2020, Wong et al., 2021), predominantly for non-surgical therapy, and to a lesser extent, following periodontal surgery also (Saito et al., 2011, Makino-Oi et al., 2016, Chou et al., 2017). Vergnes et al. (2018) found OHRQoL (using the GOHAI index) significantly improved following non-surgical therapy in a population with both type 1 and 2 diabetes (n=91), particularly in the pain perception and psychological domains. These findings have been corroborated in a more recent 6 month follow up RCT (Hsu et al., 2021). My study agrees with this finding, showing that in both the test and control group, there was a significant improvement in OHRQoL between BL and 12months (particularly in the eating, smiling and enjoying contact with others dimensions). The observation of improved OHRQoL in the control group is clearly complex and could be in part attributable to the regular supra-gingival scaling that was administered. Another explanation might be in relation to patient expectations (Carr et al., 2001). Patient expectations are modulated by their experience and are highly individual and specific, which are currently not accounted for in OHRQoL or QoL measures. If previous treatment or experience with a dentist (e.g., with an ultrasonic scaler) has led to a positive outcome, then experiencing

a similar or new intervention may also lead the patient to believe that a positive outcome will be inevitable. This could directly influence recording impacts in OHRQoL measures.

Several studies have demonstrated that OHRQoL is negatively affected by periodontitis (Needleman et al., 2004) and patients with severe periodontitis have worse OHRQoL than those with a healthy periodontium/ mild periodontitis (Ng and Leung, 2006, Durham et al., 2013). The present study was unable to find a correlation of a worse OHRQoL with severity of disease (as measured by number of sites with PPD≥5 mm), which might be explained by several reasons. Firstly, this study included a distinct cohort of patients with both severe periodontitis and poorly controlled diabetes, therefore it's possible that having a co-morbidity such as diabetes could change or overshadow a patient's experience of periodontitis and/or OHRQoL. Secondly, this study included only patients with severe forms of periodontitis, therefore, it's possible the range of cases (i.e., least severe compared with most severe) was not great enough to distinguish a difference in PROMs. Furthermore, there was no healthy control group in this study in order to compare OHRQoL with the diseased group, which was the case with previous studies (Ng and Leung, 2006, Durham et al., 2013).

Although global transition ratings are commonly used in the medical literature, they are much less commonly seen in periodontal clinical trials. One study of 45 patients (Tsakos et al., 2010), found that 38% of participants reported their periodontal health, 'improved a little', and 49% reported that it had, 'improved a lot', one month after intensive or control periodontal therapy. The present study reported similar proportions with 40.1% of all participants reporting their periodontal health, 'improved a little', and 43.9%, 'improved a lot'. The difference might be attributed to the current study having a larger sample size and a longer follow-up, thus different time point of questionnaire administration (12M).

Single- item questions for self-rated general health are less commonly reported for patients with type 2 diabetes, as there is a tendency for researchers to favour validated PROMs such as the SF-36 (Verhulst et al., 2019a) or condition-specific PROMs such as the Audit of Diabetes Dependent Quality of Life (ADDQoL) (Papazafiropoulou et al., 2015). One recent study (Umeh, 2022) analysed data from the 2017 Health Survey for England (Mindell et al., 2012), and found that in 280 adults with type 2 diabetes mellitus, self-rated general health appeared to be unconnected to glycaemic control (6.5% HbA1c used as the threshold). The study results showed that almost 50% (exact value not given) of participants with poorly controlled diabetes (HbA1c > 6.5%) reported their general health as fair or bad, which is less than we observed in my study (approximately 63% of participants), whilst the remaining participants (over 50%) reported their general health as good or very good compared with approximately 35% in my study. The reason for these differences is unclear, however it may be that the higher mean HbA1c level in my study (8.1% versus 7.4%) translated to poorer self-reported general health (Nielsen et al., 2011). Furthermore, as shown in Umeh (2022) the impact of the number and type of multi-morbidities in my study (not analysed) may have detrimentally affected self-reported general health.

Finally, using the distribution-based approach, a MID of 5.32 for CS-OIDP was estimated and a small effect size of 0.29. This closely aligns with (Tsakos et al., 2010) who found a MID of 5.22 and effect size of 0.44 (or 5.3 -5.7 using the anchor-based approach). The estimations of MID in this study appear slightly higher than that presented in the previous chapters (4 and 5), which might be expected considering a different cohort of patients as well as intervention(s). Alternatively, it could be that magnitude of change in PROMs score for a patient living with diabetes is higher than that of a patient without diabetes. Further studies would therefore be required to confirm this estimation.

Approximately 30% (n=74) of participants in this study experienced a change in PROM score equal to or above the MID. The proportion of patients experiencing a benefit appears low (as was seen in chapter 4 and 5), however it should be remembered that the MID is estimated at a group level, and the distribution-based approach in calculating the MID evaluates the probability of a moderate to large effect (taking into consideration variance of the data). The number of individuals experiencing a change greater than equal to the MID could therefore be an underestimation of the actual number who experienced a benefit.

6.5.3 Strengths and Limitations of the Study

This clinical trial has a number of strengths. The study has a large sample size and a long follow-up period of 12M. Additionally, recruitment was from a number of clinics, both public and private, within the UK enabling a variety of patients from different socio-economic, social and cultural backgrounds, more representative of the population. Unique to this study also, was the intention to reduce the load of inflammation caused by periodontitis by both non-surgical and surgical needs (where appropriate).

The limitations of this study include that it was conducted in a single university setting, with operators generally experienced in the treatment of stage III/ IV periodontitis, which may limit generalisation. Additionally, there is a potential recruitment bias in the study, thus caution must be taken in regard to generalisability of results to patients with diabetes and periodontitis in other settings. The impact of medications (excluding those used to treat diabetes) could have contributed to differences in HbA1c between the groups at 12M, considering there were some BL differences of medications (e.g., aspirin, angiotensin-II blockers and beta blockers). Furthermore, it is also unclear how these medications may have impacted OHRQoL. The time points of administering the OHRQoL questionnaires was at BL and 12M. In order to follow the trajectory of healing, which undoubtedly is different from individual to

individual, additional time points to capture OHRQoL could have provided more relevant information in regard to comparing the two treatment groups.

6.5.4 Implications for Practice and Policy

Patients with diabetes and stage III/IV periodontitis can expect that, in addition to improvement in surrogate clinical measures of periodontitis and diabetic control (HbA1c), OHRQoL will improve up to 12M after therapy. This improvement is regardless of modality of treatment (supra-gingival scaling alone, sub-gingival scaling and/or surgery). Additionally, periodontal therapy improves global ratings of general health 12M after therapy.

Cost effectiveness modelling indicates that although periodontal treatment increases overall costs associated with the management of periodontitis, the health benefits which could be gained by a reduction in HbA1c are sufficient in the majority of patients (Solowiej-Wedderburn et al., 2017). With the results of the present study, there is further benefit in regard to improvement of quality of life.

6.5.5 Implications for Further Research

There is need for quality of life research in diabetic patients with stage III/IV periodontitis undergoing treatment in the long term (>5 years), which would include supportive periodontal care. Studies on how diabetes might affect or modulate quality of life in periodontitis patients would also be important to understand our patients' journey.

6.6 Conclusions

Within the limitations of this study, I have found that periodontal therapy improves OHRQoL in patients with diabetes suffering from stage III/IV periodontitis at 12M. No correlation between the change in metabolic control

(HbA1c) and OHRQoL was found between BL and 12M post-therapy, however self-rated periodontal health was weakly correlated with general QoL.

7. PATIENT REPORTED OUTCOME MEASURES AND SUPPORTIVE PERIODONTAL CARE

7.1 Background

7.1.1 Supportive Periodontal Care

As previously outlined in Chapter 2, SPC is an important phase of therapy which should be tailored to the needs of each patient. Patients with periodontitis, ideally enter a SPC programme having reached stability in periodontal health (Chapple et al., 2018) following active periodontal therapy.

7.1.2 Long-term Supportive Periodontal Care

Professional maintenance following treatment of periodontitis has proven to be an integral part of long-term successful management of periodontally susceptible patients (Axelsson and Lindhe, 1981b, Axelsson et al., 2004b), irrespective of the modality of active therapy (Knowles et al., 1979, Badersten et al., 1981, Westfelt et al., 1985, Isidor and Karring, 1986, Badersten et al., 1987, Kaldahl et al., 1988). However, the number of well-controlled, prospective long-term (>5 years follow-up) clinical trials evidencing this is limited (Sanz-Martin et al., 2019) and a recent systematic review highlighted the lack of evidence to advocate the superiority of one approach to improve tooth maintenance during SPC (Manresa et al., 2018).

Encouragingly, evidence suggests that during SPC of up to 14 years, mean annual tooth loss due to periodontitis is low (Rosling et al., 2001, Trombelli et al., 2015), however, following the 11th European Workshop in Periodontology, it was identified that more research was required to inform on gaps in the evidence, particularly regarding treatments that work best in the phase of SPC (Sanz et al., 2015), a conclusion strengthened recently by a Cochrane review (Manresa et al., 2018).

The commitment of patients to an SPC programme regarding time, finances and compliance, is significant. Previous reviews however are less clear on what patients might expect in terms of recurrence of condition during the maintenance phase. It is therefore important to understand if SPC makes a difference to disease progression, tooth loss and quality of life in the long term, when compared with those patients who do not receive SPC (or irregularly attend).

The ideal outcome measure to assess the success of SPC compared with no SPC is tooth loss. Despite this, surprisingly few studies report tooth loss as their primary outcome, perhaps due to the extended follow up time required to report it. Disease progression at unstable sites of residual disease or disease recurrence (finding of periodontitis at a site that was rendered periodontal healthy/ stable) are more frequently reported outcomes, as measured by surrogate markers of periodontal probing depth (PPD), clinical attachment levels (CAL) and bleeding on probing (BOP).

7.1.3 Quality of life

Importantly, tooth loss often results in compromised aesthetics, difficulty chewing and speaking and has been shown to negatively impact a patient's oral health-related quality of life (Matsuyama et al., 2021). Additionally, disease progression may lead to sequelae such as tooth loss, tooth mobility, reduced masticatory function and subsequent change in food intake and once again has had a negative effect on oral health-related quality of life (Uy et al., 2022).

As highlighted above, a SPC programme requires extensive commitment from the patient specifically with regard to life-long adherence to visits and plaque control. Furthermore, thorough and careful planning of care, including risk factor management, frequency of visits, and any intervention(s) must be carried out by the clinician, thus the costs (direct, indirect and intangible) may be substantial. Intangible costs may be explored in this context using patient

reported outcomes. Due to the long-term nature of SPC, the information gained from the patient could be quite different to that following therapeutic interventions used to treat unstable disease, potentially revealing what might constitute a 'good' outcome from the patient's point of view. Outcomes which are more relevant to our patients could have an important impact, such as improved health literacy and enhanced adherence to an SPC programme, potentially leading to greater ownership of the patient to manage his/her own condition in the long term. It is therefore important to clarify benefits (if any) of regular, long-term SPC compared with no/irregular SPC regarding clinical and patient-reported outcomes.

This systematic review was commissioned by the European Federation of Periodontology (EFP) for presentation at the XVII European workshop to inform on the Stage IV periodontitis S3 guideline development. The design and outcomes were determined independently of the EWP (although some constraints were imposed e.g., English language only), and were subsequently peer-reviewed (internally) by the EWP committee. The primary focus of this research for our group was PROMs.

7.2 Aim

The aim of this systematic review was to answer two focussed questions:

Focussed question 1 (FQ-1), 'In people treated for periodontitis and in SPC for five years or more, compared with no or irregular SPC, how common is disease progression and what is their oral health-related quality of life (OHRQoL)?'

Focussed question 2 (FQ-2), 'In people treated for periodontitis and experiencing recurrence of disease, what is the effect of different methods of treatment of the recurrence as assessed by measures of health, quality of life, cost and accessibility of care, and harms?'

7.2.1 PICOS Components

Population

Participants treated for periodontitis with no age restriction. Any definition of periodontitis was included considering there have been a number of changes in the classification of periodontal diseases over recent decades.

No restriction was applied for the type of treatments carried out both in the active periodontal therapy (APT) or supportive periodontal care phases. The end of active treatments was clearly defined in terms of periodontal health status.

The focus of this systematic review was stage IV periodontitis (advanced disease with extensive tooth loss), however, in view of the recent adoption of the current classification and our expectation that severity of periodontitis would be incompletely described, we included all severities of periodontitis with a plan to analyse stage IV periodontitis separately if possible.

Intervention

Any kind of intervention that might be considered part of SPC. As SPC is a complex intervention, for the purposes of this review this may have included;

- Interview: periodontal health symptoms, medical and social history, risk factors including tobacco use, stress and diabetes and reported plaque control regime
- Assessment: plaque and calculus deposits, periodontal health including inflammation, probing pocket depths and bleeding pockets
- Formulating: intervention needs including risk factor management, oral hygiene and retreatment
- Practical Intervention: oral hygiene coaching, instrumentation of supra- and subgingival plaque and calculus, treatment of sites with

recurrence (finding of periodontitis at a previously healthy/stable site) or residual periodontitis (a deep periodontal pocket remains despite active therapy)

- Planning: interval before next SPC visit

Comparison

Studies comparing SPC with no/irregular SPC, different frequencies of SPC recall visits, different settings for SPC (specialist versus non-specialist) and SPC using adjuncts (e.g., chemical agents, locally administered antiseptics/ antibiotics and systemically administered antibiotics).

Outcome Measures

It would be impossible to distinguish the published literature between recurrence, occurrence of disease at previously healthy (non-diseased) sites and progression of residual disease at unstable sites. Recurrence means a finding of periodontitis at a site that was rendered periodontally healthy/ stable through treatment. Occurrence refers to a site within a patient diagnosed and treated for periodontitis (periodontitis case), but which did not previously show signs of disease, and progression would be characterised by deterioration (e.g., CAL loss) at a site that had residual disease despite active treatment.

Since the distinction could not be made from the existing literature, the primary outcome measures for this systematic review were 1) the proportion of patients who experienced tooth loss and, 2) change in oral health related quality of life (OHRQoL) with a validated OHRQoL tool.

It was the intention to make OHRQoL an equal primary outcome to tooth loss in the original review, however the EWP committee rejected this for the European workshop and associated publication. However, for this thesis, it has been returned to equal status of primary outcome, since the review was otherwise designed with this intent.

Secondary outcomes were 1) proportion of patients who experienced at least one site of CAL loss of 2 mm or greater; 2) number of periodontal probing pocket depths (PPD) of at least 5 mm or more with bleeding on probing; 3) number of sites that need/ experienced retreatment; 4) health economic outcomes; 5) any other patient reported outcomes (PRO).

Study Design

The search strategy included clinical studies with a prospective design (for both FQ-1 and FQ-2) in order to minimise selection bias. As FQ-2 was an intervention research question, studies were limited to randomised controlled trials, controlled trials and prospective cohorts.

7.3 Methods

7.3.1 Protocol Development and Registration

This protocol was evaluated and approved by the Scientific Committee of the XVII European Workshop on Periodontology and was prepared according to the Preferred Reporting Items for Systematic Reviews and Meta-Analyses (PRISMA) guidance (Moher et al., 2009). Details of the protocol for this systematic review were registered on PROSPERO (Unique ID: CRD42020176451).

The general topic was commissioned by the EFP to inform on the stage IV periodontitis S3 guideline.

7.3.2 Patient Involvement

This review was co-produced with a member of the British Society of Periodontology Patient Forum who contributed to design, interpretation and publication.

7.3.3 Eligibility Criteria

To conduct this systematic review, we searched for all studies which had included treatment for periodontitis and had a minimum of 5 years following the end of the APT (FQ-1). For FQ-2, the minimum follow-up for re-treatment was 12-months.

7.3.4 Literature Search

Electronic Search

A highly sensitive search strategy was formulated with an experienced librarian with consideration of previous systematic reviews related to this topic (Trombelli et al., 2015, Manresa et al., 2018, Sanz-Martin et al., 2019) using a string of medical subject headings and free-text terms (Appendix G). The reason for designing a sensitive search was that we anticipated that potentially eligible studies might not be found with a limited number of search terms or by limiting to only a few databases, as the topic is not well indexed. Therefore, we anticipated a large number of hits from the search that would require screening for eligibility. The search strategies were modelled on that devised for the MEDLINE database and subsequently modified for other databases as was needed. The search was restricted to the English language (to harmonise methods across all reviews being conducted for the European Workshop and due to time constraints) and results were downloaded to EndNote X9 (2013).

Electronic databases searched included;

Ovid MEDLINE (1946 -17 July 2021);

Ovid EMBASE Classic and EMBASE (1947 – 17 July 2021);

LILACS VHL Regional Portal (to 17 July 2021);

Cochrane Central Register of Controlled Trials (CENTRAL) (to 17 July 2021);

Dentistry and Oral Sciences Source EBSCOHost (to 17 July 2021);

CINAHL Plus EBSCOHost (1937 – 17 July 2021)

OpenGrey was searched for grey literature and the register of clinical studies at the US National Institutes of Health (www.clinicaltrials.gov) in order to identify unpublished studies which may be relevant.

7.3.5 Study Selection

Inclusion Criteria

In regard to FQ-1, the following inclusion criteria were applied:

- prospective studies (to minimise the risk of selection bias)
- minimum follow-up of 5 years in SPC (to consider outcome of disease progression/ recurrence)
- endpoint of APT and the start of SPC clearly defined

For FQ-2, the following inclusion criteria were applied:

- prospective studies
- minimum follow-up of 12 months

Exclusion Criteria

The following exclusion criteria were applied:

- Cross-sectional studies
- Retrospective studies
- Case- series

To distinguish between case-series and cohort studies (particularly with low numbers of participants), a key characteristic for exclusion was a lack of information on the method of enrolment/ participant selection (e.g. consecutive cases).

Studies which investigated solely specific systemic disease or risk factors (e.g., smoking, diabetes) or only recruited participants for periodontitis treatment or previously treated for periodontitis.

Screening

Titles and abstracts (if available) retrieved from the searches were screened by a combination of two review authors (NL, FM and SH), in duplicate and independently. Based on titles and abstracts, irrelevant studies were discarded. Full texts were obtained for the remaining studies and included those which had insufficient information in the title and abstract and if at least one reviewer included the study for the next phase of screening. Reference lists of all studies that were included for full text screening and previous reviews were screened for missing records.

Two reviewers (NL and FM) assessed the full text reports according to the inclusion criteria, in duplicate and independently. Disagreements were resolved by discussion and a third author was consulted (IN) when agreement could not be resolved. Where there were several publications from the same original study, we included the study with the longest follow up period for the relevant outcome measure. Studies that did not meet the eligibility criteria were excluded and specified reasons for exclusion (Appendix H).

7.3.6 Data Collection

Data Extraction

Data were extracted by two review authors (NL and FM), in duplicate and independently using a data extraction form on Microsoft® Excel. Disagreements were resolved by discussion and when resolution was not possible, a third reviewer was consulted (IN). In order to clarify missing or unclear data, authors were contacted (where possible).

Risk of Bias

Quality assessment was carried out by two review authors (NL and SH), in duplicate and independently. Regarding FQ-1, studies were assessed for risk of bias in relation to the phase of SPC. The included studies were assessed as prospective cohorts using a modified version Newcastle-Ottawa scale (NOS) (Wells et al., 2011) to account for single arm cohorts. The modified version of the NOS removed questions concerning control groups, therefore two domains, selection and outcome, were assessed with a maximum score possible of six. FQ-2 included studies were assessed for risk of bias using the Cochrane RoB 2.0 tool (Sterne et al., 2019) for interventional randomised controlled trials (RCT), ROBINS-I tool (Sterne et al., 2016) for interventional non-randomised controlled trials (CCT) and cohorts.

Data Synthesis

Data were entered into tables stratified by study design, and decisions on which studies to include in a meta-analysis was made depending on the similarity of chief study characteristics related to each research question (i.e., incidence of recurrence or methods of managing recurrence).

Evaluation of the included studies displayed substantial heterogeneity between publications in regard to design and reporting of outcomes in the SPC phase and in trials addressing treatment methods for disease recurrence. A qualitative report of the data was planned for those studies that could not be included in the meta-analyses.

7.3.7 Data Analysis

The number of events on the total number observed at the final assessment was used for the meta-analyses. To avoid under-estimating both tooth loss and CAL loss≥2 mm, we decided to use the ‘per protocol’ number of participants. Numerous studies reported tooth loss per participant at the end of the study. An

intention to treat approach would not be able to account for tooth loss associated with subjects during follow up, and thus risk under-estimating average tooth loss. In order to check this, an intention to treat analysis (ITT) was carried out for the primary outcome of tooth loss.

Data were grouped with respect to

a) frequency of SPC, 3 monthly (3M) or unmonitored/irregular (IRREG) and;

b) length of follow-up (FU), 5-10 years follow-up (5-10 FU) or greater than 10 years follow-up (>10 FU).

Meta-analyses were subsequently performed to determine an overall prevalence of tooth loss (primary outcome) and CAL loss (≥2 mm) (secondary outcome) at patient level. The number of events on the total number observed (per protocol) were entered into the statistical software. In regard to tooth loss, this was the number of patients who lost at least one tooth, on the total number of patients available at follow-up. For CAL loss, this was the number of patients experiencing CAL loss≥2 mm at a minimum of one site, on the total number of patients available at follow-up. In the meta-analyses, 'clusters' were formed in each subgroup (Salvi et al., 2018). One cluster was representative of one treatment arm in APT. Therefore, studies with multiple treatment arms, contributed more than one cluster. Open source software, OpenMeta[Analyst] (Wallace et al., 2012), was used for meta-analysis, and a binary random-effects model chosen. Weighted mean values and 95% confidence intervals (CI) are presented via Forest plots. A p value of <0.05 was considered statistically significant.

The degree of statistical heterogeneity between studies was assessed using the chi-square test and quantified utilising the I^2 statistical test. Subgroup and meta-regression analyses were performed to determine the effect of: a) the type of treatment in APT either regenerative (reg) or non-regenerative (non-reg), b)

frequency of SPC, 3 monthly or IRREG and c) length of follow-up, 5-10 years or greater than 10 years on tooth loss and CAL loss ≥2 mm and expressed as coefficients (COEF) and 95% confidence intervals. Meta-analysis was stratified into subgroups of reg and non-reg surgery to allow evaluation of potential differences in outcomes. The summary estimate includes both types of therapy combined.

Interpretation of the I^2 test was according to the guidance of the Cochrane Handbook (Deeks et al., 2019), as follows:

- 0% to 40%: might not be important
- 30% to 60%: moderate heterogeneity
- 50% to 90%: substantial heterogeneity
- 75% to 100%: considerable heterogeneity

Studies that could not be included in the meta-analysis were described in a narrative form and an attempt to triangulate qualitative results with that of the meta-analysis was made to assess consistency of data.

Kappa statistic was used to assess the reviewer agreement based on full-text screening, and the score interpreted using values suggested by Cohen (1960). The reviewers were calibrated with the first 10 full text publications.

7.4 Results

7.4.1 Study Selection

The search yielded a large number of records, confirming a high sensitivity and low specificity which reflected the search strategy. Based on the definition of stage III versus stage IV periodontitis (Tonetti et al., 2018), we were unable to restrict the studies to solely stage IV periodontitis cases. Studies screened gave no detail of reasons for previous extraction(s) and most used previous

classifications for defining included cases. No studies assessed patient reported outcome measures (PROMs) in long-term SPC. Additionally, there were a lack of studies which specifically addressed recurrence in SPC.

A total of 33,483 records were found through the electronic searches, and following removal of duplicates, 17,003 remained. Following screening of titles and abstracts, 258 titles remained for full-text evaluation (Figure 33).. Subsequently, 225 studies were excluded (Appendix H) for often more than one reason, however the main reason was generally recorded.

FQ-1

24 studies (Knowles et al., 1979, Axelsson and Lindhe, 1981c, Pihlstrom et al., 1983, Pihlstrom et al., 1984, Kaldahl et al., 1996a, Kaldahl et al., 1996b, Hou et al., 1997, Becker et al., 2001, Ramberg et al., 2001, Rosling et al., 2001, Serino et al., 2001a, Serino et al., 2001b, Buchmann et al., 2002, Loesche et al., 2002, Loesche et al., 2005, Orsini et al., 2008, Nygaard-Ostby et al., 2010, Crespi et al., 2011, Moder et al., 2012, Dori et al., 2013b, Cortellini et al., 2017, Cieplik et al., 2018, Petsos et al., 2019, Cortellini et al., 2020b) were included in the qualitative and quantitative analysis (Table 36 and Table 37). Studies reporting on the same population were included if each paper reported on a different but relevant outcome important for this systematic review (Pihlstrom et al., 1984, Kaldahl et al., 1996b) (Table 36). The kappa score for FQ-1 was calculated to be 0.81 for full-text screening agreement indicating almost perfect agreement (Cohen, 1960).

FQ-2

Eleven studies were included (Jenkins et al., 2000, Bogren et al., 2008, Lulic et al., 2009, Tonetti et al., 2012, Costa et al., 2015, Killeen et al., 2018, Angst et al., 2019, Jasa et al., 2020, Mendez et al., 2021, Andere et al., 2022, Killeen et al., 2022) (Table 38). These were qualitatively analysed due to heterogeneity

particularly in types of intervention. The kappa score for full-text screening for FQ-2 was calculated to be 0.62 indicating substantial agreement (Cohen, 1960).

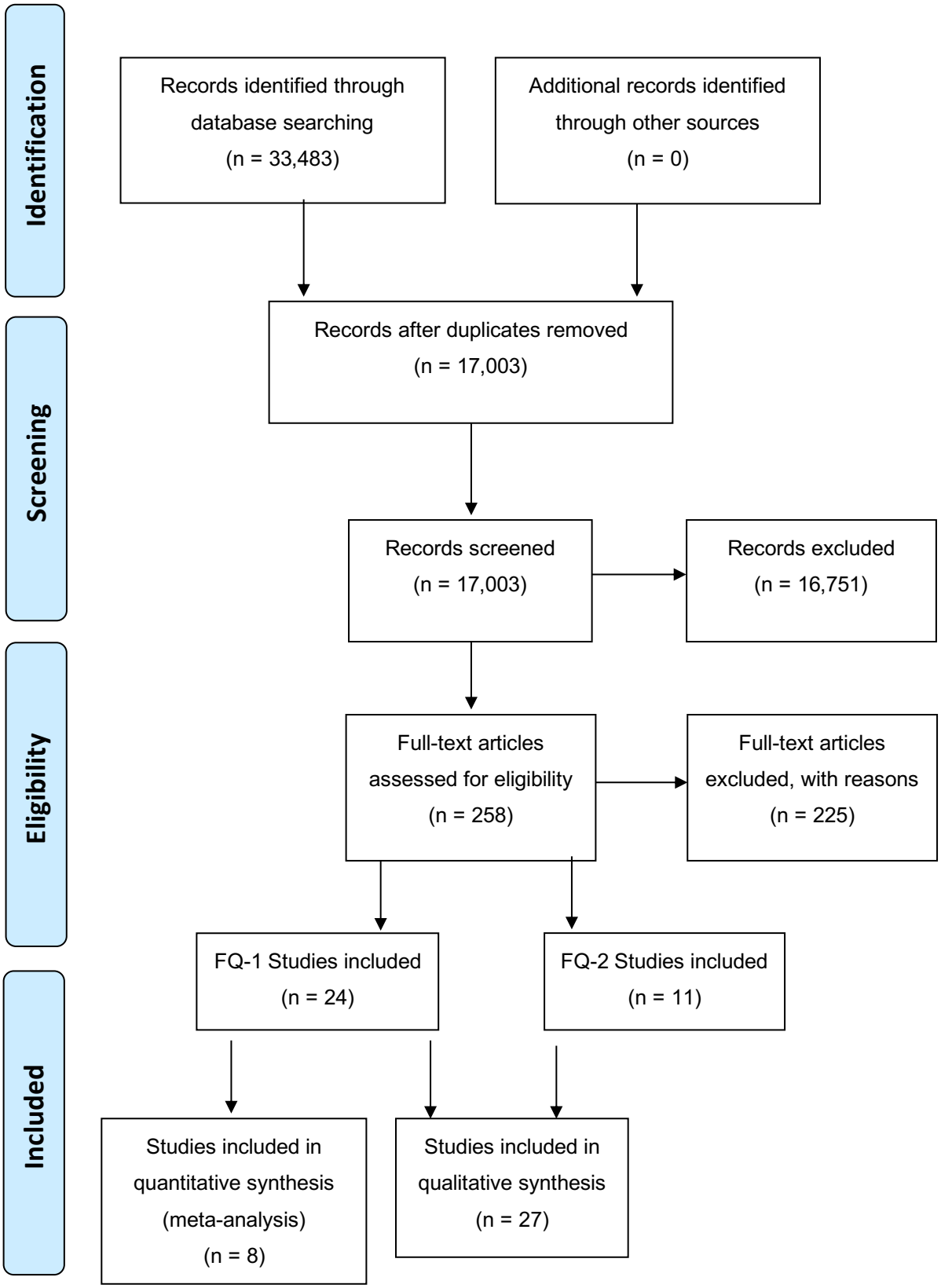


Figure 33. Study Flowchart

Table 36. Focussed Question -1: Characteristics of included studies

Publication	Country	Setting	Funding	Diagnosis	APT
Axelsson & Lindhe 1981	Sweden	University	NR	Adv. periodontal disease	Surgery: MWF in all four quadrants
Becker et al. 2001	USA	University	NR	Mod-Adv. adult periodontitis	Split mouth (RCT) a; SRP with LA b; Surgery: osseous recontouring c; Surgery: MWF
Buchmann et al. 2002	Germany	University	NR	Aggressive periodontitis	Surgery: MWF in all four quadrants
Cieplik et al. 2018	Germany	University	Partly supported by Robert Matheys Foundation (Bettlack Switzerland)	Aggressive / chronic periodontitis	Split mouth (RCT) a; GTR + ß-TCP granules (soaked in blood) b; GTR + ß-TCP granules (soaked in APC)
Cortellini et al. 2017	Italy	Private Practice	Partly supported by Accademia Tosacana di Ricerca Odontostomatologica, Italy European Research Group	NR (angular defects)	RCT a; Surgery: MWF b; Surgery: MPPT with e-PTFE c; Surgery: Flap with e-PTFE

Publication	Country	Setting	Funding	Diagnosis	APT
			on Periodontology, Genova, Italy		
Cortellini et al. 2020	Italy	Private Practice	Partly supported by the European Research Group on Periodontology (ERGOPerio), Berne, Switzerland	Stage III/IV periodontitis (generalised)	RCT (only one arm assessed for this review) Surgery: PPF (Membrane or EMD/ Membrane+xenograft/ EMD+alloplast or EMD+membrane)
Crespi et al. 2011	Italy	Private Practice	NR	Mod-Adv. adult periodontitis	Split mouth a; Surgery: MWF (quadrant) b; Surgery: CAF + CO_2 laser root conditioning
Dori et al. 2013	Hungary	University	NR	Adv. chronic periodontitis	RCT a; Surgery: EMD + xenograft b; Surgery: EMD+ ß-TCP granules
Hou et al. 1997	Taiwan	University	NR	Mod-Adv. adult periodontitis	SRP with LA
Kaldahl et al. 1996a	USA	University	NIH-NIDR grant DE06103	Mod-Adv. adult periodontitis	Split mouth (RCT) a; coronal scaling b; SRP with LA c; Surgery: MWF d; Surgery: osseous

Publication	Country	Setting	Funding	Diagnosis	APT
					recontouring
Kaldahl et al. 1996b	USA	University	NIH-NIDR grant DE06103	Mod-Adv. adult periodontitis	As above (same population)
Knowles et al. 1979	USA	University	Partly supported by US Public Health Service Grant DE 02731	Mod-Adv. adult periodontitis	Split mouth (RCT), half mouth a; Surgery; Pocket elimination, curettage b; Surgery: MWF, curettage c; Surgery; MWF, pocket elimination
Loesche et al. 2002	USA	University	US Public Health Service Grant DE-06030 from the National institute of Dental and Craniofacial Research	Adv. periodontal disease (chronic/ adult/ aggressive/ early onset)	RCT a; NST + placebo (systemic) b; NST + Metronidazole (systemic) c; NST + Doxycycline (systemic)
Loesche et al. 2005	USA	University	US Public Health Service Grant DE-06030 from the National institute of Dental and Craniofacial Research	Adv. periodontal disease (chronic/ adult/ aggressive/ early onset)	As above (same population)

Publication	Country	Setting	Funding	Diagnosis	APT
Moder et al. 2012	Germany	University	Robert Matheys Stiftung (RMS Foundation, Bettlach, CH)	Aggressive/chronic periodontitis	Split mouth (RCT) a; GTR + ß-TCP granules (soaked in blood) b; GTR + ß-TCP granules (soaked in APC)
Nygaard-Ostby et al. 2010	Norway	Private Practice	Supported by grant from Atrix Laborators Inc., Fort Collins, CO, USA	Chronic periodontitis (+ angular defect)	RCT a; Surgery: Autogenous bone graft b; Surgery: Autogenous bone graft + GTR
Orsini et al. 2008	Italy	Unclear	National Research Council (CNR), Finalized Project Materials Tailored for Advanced Technologies PF MSTA II, Ministry of University, Research, Science and Technology (MURST) Italy	NR (angular defect)	Split mouth (RCT) a: Surgery: Autogenous bone graft + resorbable membrane b: Surgery: Autogenous bone graft + calcium sulphate graft
Petsos et al. 2019	Germany	University	Partly by Moessner Stiftung research grant	Severe chronic periodontitis (+ angular defect)	RCT a: Surgery: OFD b: Surgery: OFD +

Publication	Country	Setting	Funding	Diagnosis	APT
			(Frankfurt am Main, Germany) to the Centre for Dentistry and Oral Medicine (Carolinum)		resorbable membrane
Pihlstrom et al. 1983	USA	University	NR	Mod-Adv. adult periodontitis	Split mouth (RCT) a: SRP with LA b: Surgery: MWF
Pihlstrom 1984	USA	University	NR	Mod-Adv. adult periodontitis	As above (same population)
Ramberg et al. 2001	Sweden	University	Grants from NIDCR (DE-12861) and Colgate Technology Centre, NJ USA	Adv. periodontitis	a: SRP b: SRP + Tetracycline (systemic)
Rosling et al. 2001	Sweden	University and 12 Community Dental Clinics	Supported by grants from NIDCR (DE-12861) and Colgate Technology Centre, NJ, USA	Adv. periodontitis or normal prevalence of periodontal disease	NST
Serino et al.	Sweden	University	Colgate	Adv. periodontal disease	NST + Metronidazole

Publication	Country	Setting	Funding	Diagnosis	APT
2001a			Technology Centre, NJ, USA and NIDCR (DE-12861) Bethesda, Maryland USA		(systemic) + Amoxycillin (systemic)
Serino 2001b	Sweden	University	NIDCR (DE-12861) and Colgate Technology Centre, NJ, USA	Adv. periodontal disease	RCT a: SRP b: Surgery: MWF

NR: Not reported Adv.: advanced, Mod-Adv.: moderate to advanced, MWF: Modified Widman Flap, RCT: randomised controlled trial, SRP: scaling and root planing, NST: non-surgical therapy, LA: local anaesthetic, GTR: guided tissue regeneration, ß-TCP: Beta tricalcium phosphate, APC: autogenous platelet concentrate, MPPT: modified papilla preservation technique, e-PTFE: expanded-polytetrafluorethylene membrane, EMD: enamel matrix derivative, PPF: papilla preservation flaps, CAF: coronally advanced flap, CO_2: carbon dioxide, OFD: open flap debridement

Table 37. Focussed Question -1: Characteristics of study which are related to supportive periodontal care (SPC)

Publication	Participants entering SPC (n)	Recall intervals (m = months)	Follow Up in SPC (months)	Description	Outcomes
Axelsson & Lindhe 1981	77	0-2yrs – 2m 3-6yrs – 3m	72	- Oral hygiene reviewed. Bass method of brushing, floss, toothpicks advocated. - Supra- and subgingival scaling as required.	Tooth loss (mean) CAL loss (%) PPD (mean) FMBS
Becker et al. 2001	16	0-5yrs – 3m	60	- Oral hygiene reviewed - SRP (1hr) & polish with fluoride e paste.	Tooth loss CAL (mean, %) PPD (mean) GI (mean)
Buchmann et al. 2002	13	0-5yrs – 3-6m	60	-Oral hygiene reviewed - Subgingival instrumentation if PPD>4 mm +BOP	CAL (mean, no. of sites) PPD (mean) BOP (%) GI (mean)
Cieplik et al. 2018	22	3m	144	Not reported	Tooth loss CAL (median) PPD (median)
Cortellini et al. 2017	45	3m	240	-Oral hygiene reviewed -Increased PPD≥2 mm (BOP) and CAL loss≥2 mm, adjunctive periodontal therapy consisting	Tooth loss CAL (mean) PPD (mean) FMBS (%)

Publication	Participants entering SPC (n)	Recall intervals (m = months)	Follow Up in SPC (months)	Description	Outcomes
				of non-surgical root planing, flap surgery or regenerative surgery as indicated.	Sites requiring re-tx Health economics
Cortellini et al. 2020	25	3m	108	Not reported	Tooth loss CAL (mean) PPD (mean) OHIP Health economics Other PROs
Crespi et al. 2011	25	6m	114	-Oral hygiene reviewed -coronal scaling, polishing & subgingival instrumentation as needed	PPD (mean) GI
Dori et al. 2013	22	3-6m	108	-Occlusal adjustment as needed -Oral hygiene reviewed -supra- and subgingival scaling and polishing (tailored)	CAL (mean) PPD (mean) BOP (per tooth)
Hou et al. 1997	51	1-3m	66	-Oral hygiene reviewed -Repeated instruments where required	CAL (mean) PPD (mean) GI

Publication	Participants entering SPC (n)	Recall intervals (m = months)	Follow Up in SPC (months)	Description	Outcomes
Kaldahl et al. 1996a	82	3m	84	-Sites ≥3 mm CAL loss received SRP	Tooth loss CAL (mean) PPD (mean) FMBS Other PROs
Kaldahl et al. 1996b	82	3m	84	-Oral hygiene reviewed -Supra- and subgingival instrumentation as needed	CAL (yearly incidence %)
Knowles et al. 1979	78	3m	96	Not reported	CAL (mean)
Loesche et al. 2002	90	3m	61.2 (median)	- Oral hygiene reviewed. Bass method of brushing, floss, toothpicks advocated. - Full mouth instrumentation - Recurrent sites – 1 week of unsupervised systemic metronidazole or placebo	Tooth loss (range per patient and total number) Patients requiring surgery (mean per patient)
Loesche et al. 2005	90	3m	76.8 (median)	- Oral hygiene reviewed. Bass method of brushing, floss, toothpicks advocated. - Full mouth instrumentation	Pts requiring surgery (mean per patient)

Publication	Participants entering SPC (n)	Recall intervals (m = months)	Follow Up in SPC (months)	Description	Outcomes
				- Recurrent sites – 1 week of unsupervised systemic metronidazole or placebo	
Moder et al. 2012	25	0-1yr – 3m (Univ.) 2-7yrs – 1) 6m (Univ.) or 2) private practice (not recorded)	72	Not reported	Tooth loss CAL (median) PPD (median) PBI
Nygaard-Ostby et al. 2010	40	3,4 or 6m	111	-Oral hygiene reviewed -SRP and polished as needed. Fluoride application and pts advised to use daily 0.05% NaF mouth-rinse	Tooth loss CAL (mean) PPD (mean) PBI
Orsini et al. 2008	12	3m	66	-Oral hygiene reviewed -Instrumentation as needed	Tooth Loss CAL (mean) PPD (mean) FMBS
Petsos et al. 2019	14	Unmonitored	228	Not reported	Tooth Loss CAL (mean) PPD (mean)

Publication	Participants entering SPC (n)	Recall intervals (m = months)	Follow Up in SPC (months)	Description	Outcomes
					GBI
Pihlstrom et al. 1983	17	3-4m	72	-Oral hygiene reviewed -Supra- and subgingival instrumentation	CAL (mean) PPD (mean)
Pihlstrom et al. 1984	17	3-4m	72	-Oral hygiene reviewed -Supra- and subgingival instrumentation	Tooth loss CAL (mean) PPD (mean)
Ramberg et al. 2001	115 (34 periodontitis patients)	3-4m	144	-Oral hygiene reviewed -Sites of PPD≥5 mm + BOP received subgingival instrumentation under local anaesthetic	Tooth loss (mean) CAL PPD (mean) FMBS
Rosling et al. 2001	334 (Highly susceptible group, HSG – 109/ Normal group, NG – 225)	3-4m (HSG) 6-12m (NG)	156	HSG: -Oral hygiene reviewed -Sites of PPD≥5 mm + BOP received subgingival instrumentation under local anaesthetic -Teeth that at any recall, had advanced mobility or abscess were extracted	Tooth loss (mean) CAL (mean) Sites with increase of PPD ≥2 mm (%) No. of pts with increase of CAL≥2 mm

Publication	Participants entering SPC (n)	Recall intervals (m = months)	Follow Up in SPC (months)	Description	Outcomes
Serino et al. 2001a	20	3-4m	60	-Oral hygiene reviewed -Sites of PPD≥5 mm + BOP received subgingival instrumentation under local anaesthetic -Teeth that at any recall, had advanced mobility or abscess were extracted	Tooth loss (mean) CAL (mean) PPD (mean) FMBS
Serino et al. 2001b	64	3-4m	144	-Oral hygiene reviewed -Sites of PPD≥5 mm + BOP received subgingival instrumentation under local anaesthetic -Teeth that at any recall, had advanced mobility or abscess were extracted	Tooth loss (mean) CAL (mean) PPD (mean) FMBS

yrs: years, CAL: clinical attachment level, PPD: periodontal probing pocket depth, FMBS: full mouth bleeding score, GI: gingival index, SRP: scaling and root planing, BOP: bleeding on probing, re-tx: re-treatment, OHIP: oral health impact profile questionnaire, PRO: patient reported outcomes, Univ.: university setting, PBI: papillary bleeding index, NaF: Sodium fluoride, GBI: gingival bleeding index

Table 38. Focussed Question -2: Characteristics of Included Studies

Publication	Country	Setting	Funding	- Diagnosis - Inclusion Criteria	Study Design	Intervention
Andere et al. 2022	Brazil	University	Research funding agency from Sao Paulo State (FAPESP), Brazil (grant #2016/15143-0 and 2017/05101-0)	- Stage III/IV Grade C -≥ one PPD on a single rooted tooth with both PPD and CAL≥5 mm + BOP <35 years old	RCT	**Test:** NST + photosensitizer dye (methylene blue) + PDT (1 min), washed, then diode laser beam (wavelength 660nm) – days 1, 2, 7 and 14 after NST. **Control:** Open flap debridement using modified papilla preservation flap. Hand and ultrasonic used for debridement.
Angst et al. 2019	Brazil	University	National Counsel of Technological and Scientific Development (CNPq #479288/2011-9)	- Moderate to severe periodontitis - ≥35 years old, ≥12 teeth, completed APT 3 months prior	RCT	**Test:** Full mouth oral prophylaxis (including supragingival debridement of any calculus/ biofilm up to the gingival margin, dental polishing and

Publication	Country	Setting	Funding	- Diagnosis - Inclusion Criteria	Study Design	Intervention
						OHI given based on plaque and/or marginal bleeding) **Control:** Full mouth oral prophylaxis (including OHI + subgingival instrumentation, no LA) at all sites.
Bogren et al. 2008	Multi-centre (Sweden, USA)	Specialist Private Practice & University	Part funded by National Institute of Dental and Craniofacial Research (Bethesda, Maryland)	- Moderate-advanced periodontitis - Minimum of 4 teeth with PPD≥5 mm	RCT	**Test:** Instrumentation + 8.8% doxycycline gel in PPD≥5 mm at BL, 1 and 2 years. **Control:** Instrumentation alone (PPD≥5 mm)
Costa et al. 2015	Brazil	Private Practice	Grants from Minas Gerais State Foundation & National Counsel of Technological	- Moderate-advanced chronic periodontitis - Minimum 4 sites	Prospective Cohort	**RC:** 96 subjects, **IC:** 116 subjects Instrumentation (NST or ST, when appropriate). ST

Publication	Country	Setting	Funding	- Diagnosis - Inclusion Criteria	Study Design	Intervention
			and Scientific Development	with PPD≥5 mm and CAL≥3 mm, BOP and/ suppuration		when PPD≥5 mm + BOP (45-60 days after NST). Compared treatment of recurrence via NST or ST in RC and IC groups.
Jasa et al. 2020	USA	University	Windsweep Farm Fund (Lincoln, NE) and Dr. and Mrs. Mick Dragoo (Escondido, CA)	- Stage III/ IV periodontitis grade B -40-85 years old, one quadrant with ≥3 posterior teeth + one 6-9 mm interproximal PPD	RCT	**Test:** papilla reflection/ root planing, fiberoptic assessment, etching +EMD **Control:** papilla reflection/ root planing, fiberoptic assessment, etching + saline
Jenkins et al. 2000	UK	University	NR	NR - Minimum of 4 sites with PPD≥4 mm and persistent BOP	CCT	**Test:** Subgingival scaling at 3, 6 and 9 months **Control:** Coronal scaling only (and for any sites with CAL≥2

Publication	Country	Setting	Funding	- Diagnosis - Inclusion Criteria	Study Design	Intervention
						mm, but excluded from analysis), at 3, 6 and 9 months
Killeen et al. 2018	USA	University	- Dr D. H. Reinhardt Scholar Program - Dr. Mick Dragoo and wife Mary and the Nebraska Dental Association Foundation	- One posterior interproximal PPD≥5 mm with history of BOP	RCT	**Test:** NST + 1mg of Minocycline microspheres (local application) at 0, 6, 12 and 18 months **Control:** NST alone
Killeen et al. 2022	USA	University	Windsweep Farm Fund (Lincoln NE)	-Stage III Grade B - one interproximal site of 6-9mm PPD, history of BOP and no vertical bone loss ≥1.5mm	RCT	**Test:** Surgical papilla reflection + NST+ SIM+MCL **Control:** Surgical papilla reflection + NST + MCL alone
Lulic et al. 2009	Switzerland	University	Part supported by HEL-Bos Photodynamic Systems GmbH, Austria and by the Clinical Research	- Single PPD≥5 mm with/out concomitant BOP	RCT	**Test:** NST + photosensitizer dye (phenothiazine chloride) + PDT (diode laser, wavelength 670nm

Publication	Country	Setting	Funding	- Diagnosis - Inclusion Criteria	Study Design	Intervention
			Foundation (CRF) for the Promotion of Oral Health, Switzerland			and power density 75mW/cm^2) **Control:** NST + photosensitizer dye (phenothiazine chloride)
Mendez et al. 2021	Brazil	University	See Angst et al. 2019	See Angst et al. 2019 - Stage III periodontitis (n=23) and Stage IV periodontitis (n=39)	RCT	See Angst et al. 2019
Tonetti et al. 2012	Multi-centre (Italy, Germany, Greece, Netherlands, Switzerland)	Private Practice & University	European Research Group on Periodontology (ERGOPerio) with an unrestricted grant from IVOCLAR Vivadent (Liechtenstein). Doxycycline gel provided by	- Moderate-severed periodontitis - Minimum 4 teeth with residual PPD≥5mm and BOP	RCT	**Test:** Instrumentation + 14% doxycycline gel in PPD≥4 mm at BL. **Control:** Instrumentation alone (PPD≥4 mm)

Publication	Country	Setting	Funding	- Diagnosis - Inclusion Criteria	Study Design	Intervention
			IVOCLAR.			

RCT: randomised controlled trial, PPD: periodontal probing pocket depth, CAL: clinical attachment level, BL: baseline, BOP: bleeding on probing, NR: not reported, CCT: controlled clinical trial, RC: regular compliers, IC: irregular compliers, NST: non-surgical therapy, ST: surgical therapy, mg: milligram, PDT: photodynamic therapy, nm: nanometres, mW/cm^2: milliwatt per square centimetre, SIM: simvastatin gel, MCL: methylcellulose (carrier

7.4.2 Population

We were unable to find data on stage IV periodontitis or that could be analysed as such. Studies reported an initial diagnosis of periodontitis with some further describing as moderate and severe disease. Types of diagnosis reported in the articles included, 'advanced periodontal disease', 'moderate to advanced adult periodontitis', 'aggressive periodontitis', 'chronic periodontitis', 'advanced chronic periodontitis', and 'severe chronic periodontitis'. One recently published study (Cortellini et al., 2020b) referred to the population as, 'stage III or IV periodontitis' in a retrospective manner, as recruitment was prior to the publication of the most recent classification (Table 36).

7.4.3 Supportive Periodontal Care

Description of SPC

When assessing the elements carried out in the phase of SPC, the majority of studies included brief description of oral hygiene review and re-enforcement in conjunction with focussed supra- and subgingival instrumentation (Axelsson and Lindhe, 1981c, Pihlstrom et al., 1983, Pihlstrom et al., 1984, Kaldahl et al., 1996a, Kaldahl et al., 1996b, Hou et al., 1997, Becker et al., 2001, Ramberg et al., 2001, Rosling et al., 2001, Serino et al., 2001a, Serino et al., 2001b, Buchmann et al., 2002, Loesche et al., 2002, Loesche et al., 2005, Orsini et al., 2008, Nygaard-Ostby et al., 2010, Crespi et al., 2011, Dori et al., 2013b, Cortellini et al., 2017). Five publications did not describe any detail about recall visits (Knowles et al., 1979, Moder et al., 2012, Cieplik et al., 2018, Petsos et al., 2019, Cortellini et al., 2020b).

Nine studies provided some description of the operator(s) who carried out the SPC visits (Knowles et al., 1979, Axelsson and Lindhe, 1981c, Pihlstrom et al., 1984, Rosling et al., 2001, Loesche et al., 2002, Loesche et al., 2005, Nygaard-

Ostby et al., 2010, Cortellini et al., 2017, Cieplik et al., 2018) although level of experience was not advised.

No studies specifically addressed risk factor control in regard to smoking cessation or glycaemic control advice. Details of the factors which influenced recall interval length were not given in any study.

Recall Intervals

All studies reported on the frequency of recall intervals, with the majority of studies applying 3 monthly visits. However, there was some variability between studies, with the shortest interval being 1-3 months (Hou et al., 1997) and the longest being up to 12 months (Rosling et al., 2001) based on a perceived disease risk by the attending dentist (details not specified). Some studies reported a more frequent recall plan in the first 1-2 years after APT (Axelsson and Lindhe, 1981c, Buchmann et al., 2002, Moder et al., 2012, Cieplik et al., 2018), thereafter reducing the frequency with tailored SPC intervals.

Length of Follow-Up

The minimum follow-up period in SPC to be included in this review was 5 years. Seventeen studies had a follow-up of 5-10 years (Knowles et al., 1979, Axelsson and Lindhe, 1981c, Pihlstrom et al., 1983, Pihlstrom et al., 1984, Kaldahl et al., 1996b, Kaldahl et al., 1996a, Hou et al., 1997, Becker et al., 2001, Serino et al., 2001a, Buchmann et al., 2002, Loesche et al., 2002, Loesche et al., 2005, Orsini et al., 2008, Nygaard-Ostby et al., 2010, Moder et al., 2012, Dori et al., 2013b, Cortellini et al., 2020b). Seven studies (Ramberg et al., 2001, Rosling et al., 2001, Serino et al., 2001b, Crespi et al., 2011, Cortellini et al., 2017, Cieplik et al., 2018, Petsos et al., 2019) had SPC follow-up periods greater than 10 years. Two studies reported on 20 years of follow-up (Cortellini et al., 2017, Petsos et al., 2019).

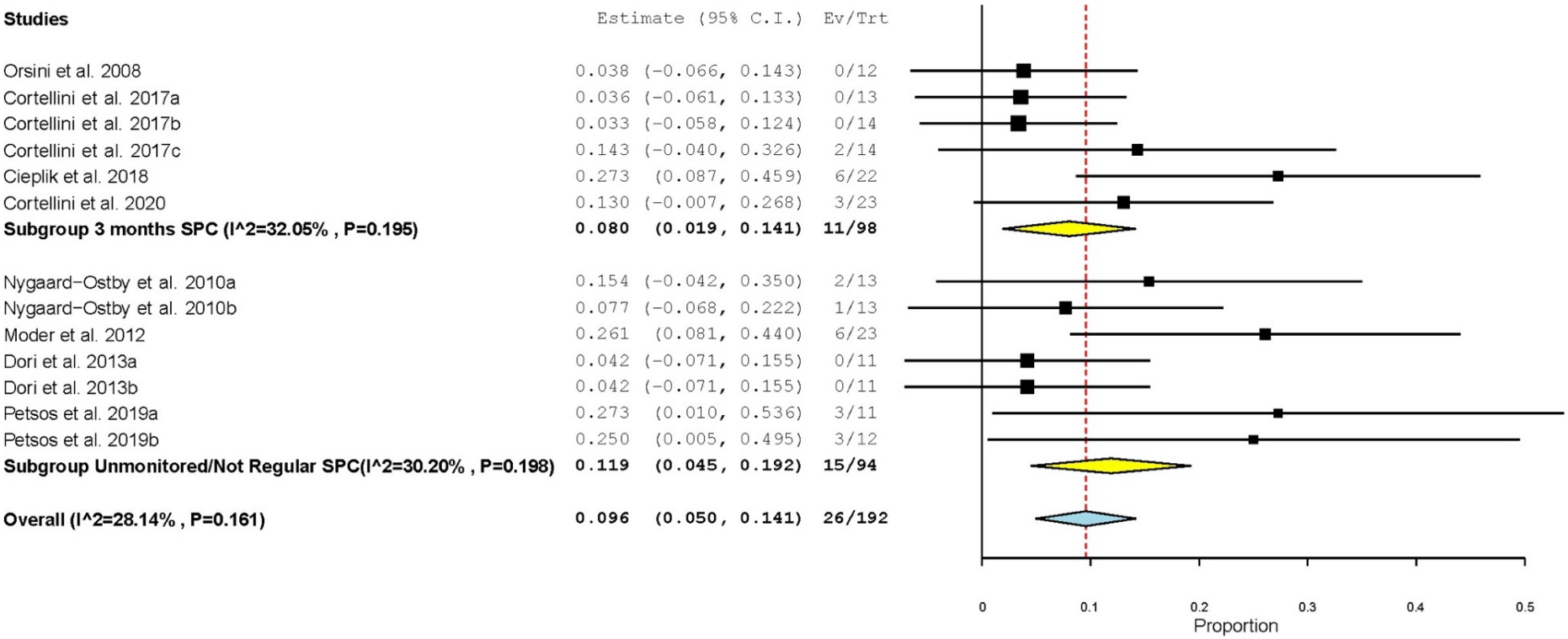
7.4.4 Meta-Analyses

Tooth Loss

Eight studies addressing FQ-1 contributed data for estimating tooth loss at patient level (Orsini et al., 2008, Nygaard-Ostby et al., 2010, Moder et al., 2012, Dori et al., 2013b, Cortellini et al., 2017, Cieplik et al., 2018, Petsos et al., 2019, Cortellini et al., 2020b). Data were sub-grouped according to treatment arms in APT, culminating in a) six clusters for patients in the 3M subgroup and seven clusters in the IRREG subgroup; and b) seven clusters for patients in the 5-10 FU subgroup and six clusters in the >10 FU subgroup. The per protocol meta-analysis at patient level for tooth loss, observed 192 participants (Figure 34).

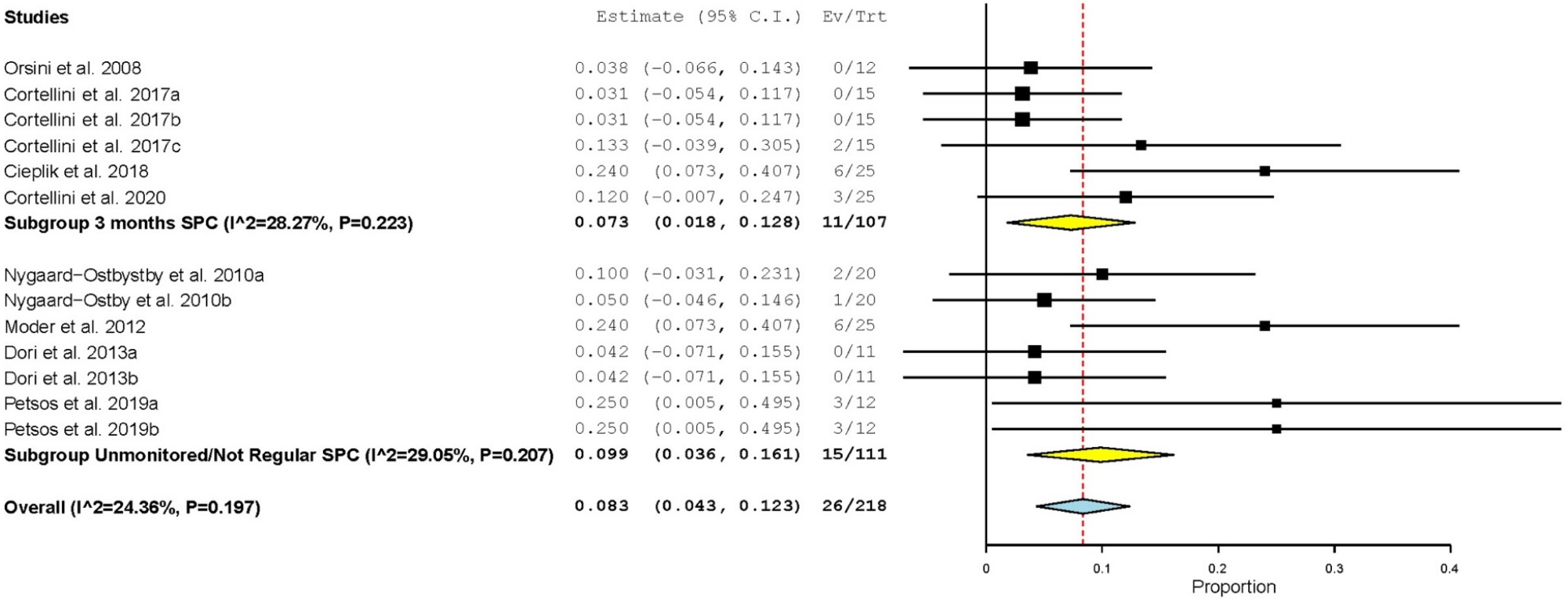
The 3M subgroup included 98 participants, whilst the IRREG subgroup observed 94. The proportion of patients experiencing tooth loss overall yielded a weighted value of 9.6% (95% CI 5-14%), with low heterogeneity I^2=28% (p=0.161). Subgroup analysis showed a weighted mean value for the 3M group as 8% (95% CI 2-14%), with low-moderate heterogeneity I^2=32% (p=0.195), whilst the IRREG group displayed a 11.9% (95% CI 5 - 19%) prevalence, low-moderate heterogeneity I^2 30.2% (p=0.198).

The ITT meta-analysis included a total of 218 participants (Figure 35). The 3M subgroup had 107 patients, and the IRREG subgroup included 111. As anticipated, the percentages were less than the per protocol analysis. Overall, the proportion of patients experiencing tooth loss was 8.3% (95% CI 4.3-12.3%) and low heterogeneity (I^2=24%, p=0.197). The subgroup analysis found that the 3M group displayed a prevalence of 7.3% (95% CI 1.8-12.8%) and low heterogeneity, I^2=28% (p=0.223), whilst the IRREG group was 9.9% (95% CI 3.6-15.1%) with low heterogeneity once again, I^2=29% (p=0.207).



F-UP = follow-up; C.I. = confidence interval; Ev = events; Trt = treatment group (i.e., total number of patients in the group)

Figure 34. Forest plot of the proportion of patients who experienced tooth loss according to frequency of supportive periodontal care (SPC) - per protocol.



F-UP = follow-up; C.I. = confidence interval; Ev = events; Trt = treatment group (i.e., total number of patients in the group

Figure 35. Forest plot of the proportion of patients who experienced tooth loss according to frequency of supportive periodontal care (SPC) - intention to treat.

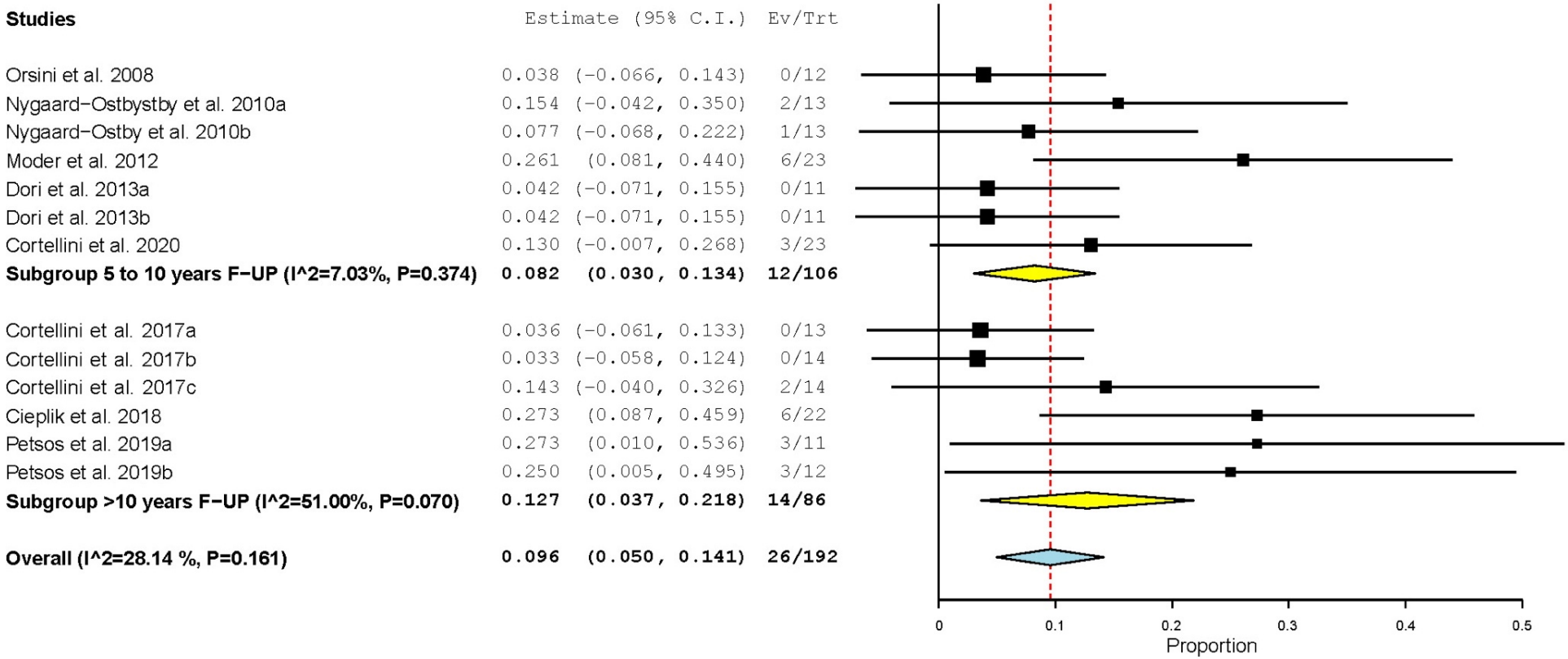
Length of follow-up time was also considered at patient level for tooth loss (Figure 36), 106 participants were observed in the 5-10 FU subgroup and 86 in the >10 FU subgroup. The weighted value for tooth loss was 8.2% (95 CI 3%-13%) for the 5-10 FU group and 12.7% (95% CI 4-22%) for >10 FU group, with substantial heterogeneity I^2 test 70% (p=0.374) and 51% (p=0.070) respectively.

The ITT analysis according to follow-up time at patient level (Figure 37) observed 124 participants in the 5-10 FU subgroup and 94 in the >10 FU subgroup. The proportion of patients experiencing tooth loss for the 5-10 FU group was 7.3% (95% CI 2.9-11.7%) and for the >10 FU group was 11.5% (95% CI 3.2-19.9%), with no heterogeneity detected I^2=0% (p=0.453) and substantial heterogeneity I^2 test 50% (p=0.073) respectively.

Meta-regression analyses were performed to investigate the influence of type of treatment in APT (regenerative or non-regenerative), frequency of SPC (3M or IRREG) and length of follow-up (5-10 FU or >10 FU) on tooth loss. There was no evidence of an association between type of treatment (COEF 0.1; 95% CI -0.07 – 0.3, p=0.249), frequency of SPC (COEF 0.05; 95% CI - 0.05 - 0.1, p=0.341) or length of follow-up (COEF 0.02; 95% CI -0.08 – 0.1, p=0.704) and tooth loss was found.

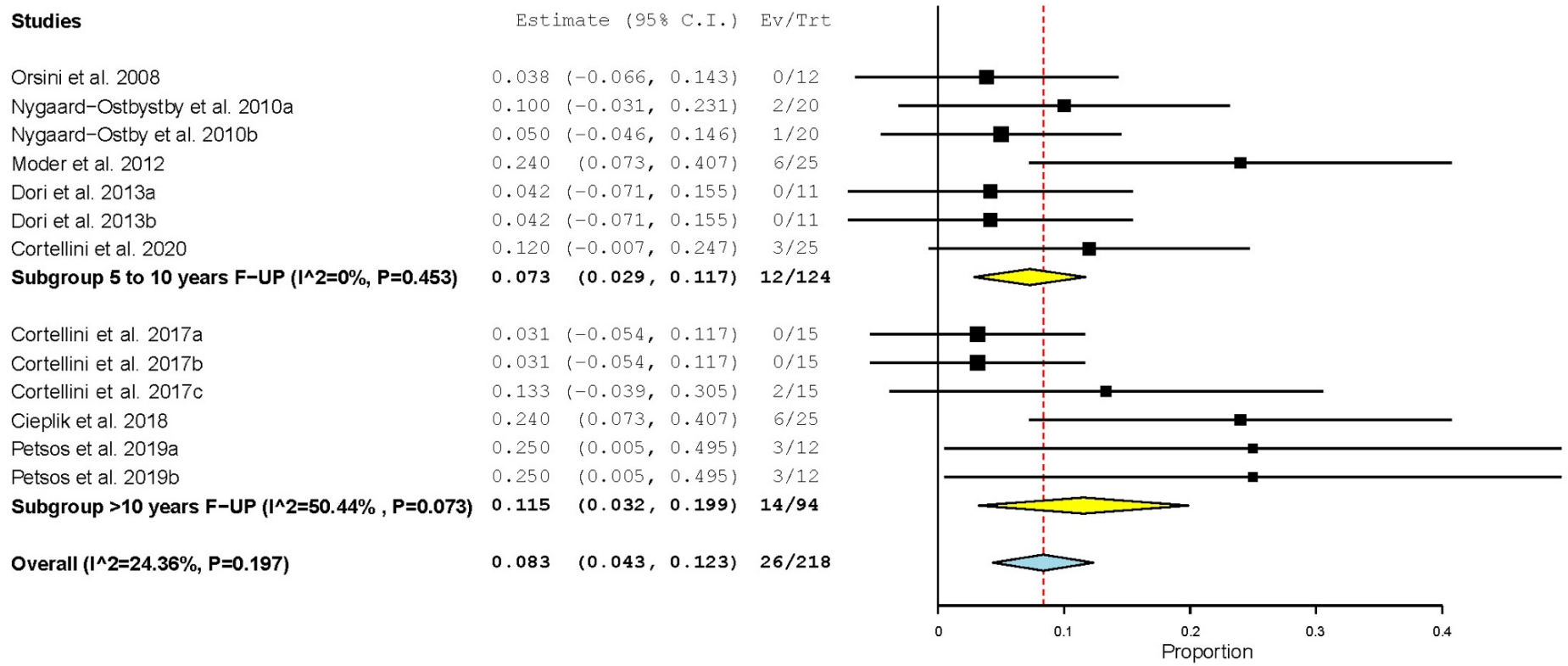
Clinical Attachment Level loss (≥2 mm)

Three studies for FQ-1 contributed data for estimating the number of patients experiencing CAL loss ≥2 mm (Dori et al., 2013b, Cortellini et al., 2017, Petsos et al., 2019). Data were sub-grouped according to treatment arms in the APT, culminating in a) three clusters for patients in the 3M subgroup and four clusters in the IRREG subgroup; and b) two clusters for patients in the 5-10 FU subgroup and five clusters in the >10 FU subgroup. The meta-analysis for patients experiencing CAL loss ≥2 mm, observed 86 participants (Figure 38).



F-UP = follow-up; C.I. = confidence interval; Ev = events; Trt = treatment group (i.e., total number of patients in the group)

Figure 36. Forest plot of the proportion of patients who experienced tooth loss according to length of follow up (per protocol).



F-UP = follow-up; C.I. = confidence interval; Ev = events; Trt = treatment group (i.e., total number of patients in the group)

Figure 37. Forest plot of the proportion of patients who experienced tooth loss according to length of follow up (intention to treat).

The 3M subgroup observed 41 participants, whilst the IRREG subgroup observed 45. The proportion of patients experiencing at least one site of CAL loss≥2 mm overall yielded a weighted mean value of 24.8% (95% CI 11-38%), with substantial heterogeneity I^2 =63% (p=0.013). Subgroup analysis showed a weighted mean value for the 3M group as 30.2% (95% CI -2-63%), I^2 = 87% (p<0.0001), whilst the IRREG group displayed a 21.4% (95% CI 10-33%) prevalence, I^2 0% (p=0.884). The difference between the groups was not statistically significant (p=0.332).

Length of follow-up time was assessed at a patient level for CAL loss ≥2 mm (Figure 39), with 22 participants observed in the 5-10 FU subgroup and 64 in the >10 FU subgroup. The proportion of patients experiencing at least one site of CAL loss ≥2 mm was 22.1% (95% CI 5-39%) for the 5-10 FU group and 26.3% (95% CI 8-45%) for >10 FU group I^2 = 0% (p=0.609) and 75% (p=0.003) respectively.

The random effects meta-regression analyses found no association between frequency of SPC (COEF 0.13; 95% CI -0.1 – 0.4, p=0.332) and length of follow-up (COEF -0.16; 95% CI -0.5 – 0.2, p=0311) with percentage of patients experiencing CAL loss≥2 mm, however the type of treatment carried out in APT (regenerative or non-regenerative) was significantly associated (COEF 0.26; 95% CI 0.01 – 0.5, p=0.043), whereby a non-regenerative intervention was more likely to experience greater proportion of patients with CAL loss≥2 mm. Therefore, the estimate of the prevalence of patients with CAL loss≥2 mm would be expected to increase by 0.26 when non-regenerative treatment was carried out in APT according to this random effects meta-regression model.

7.4.5 Qualitative Analyses

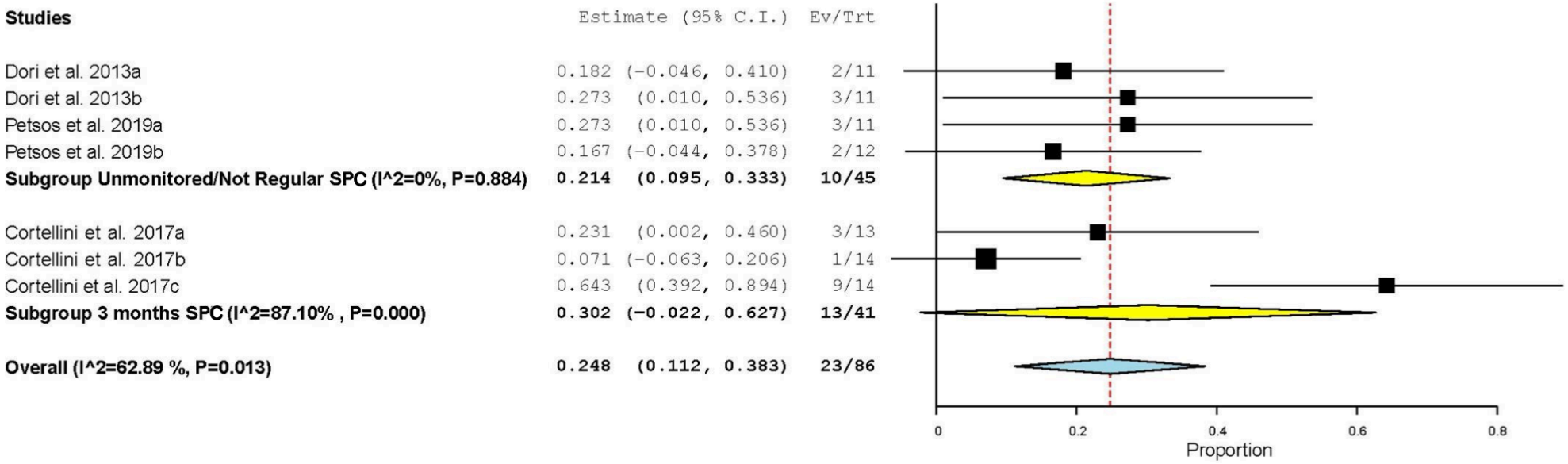
Tooth Loss

FQ-1

Tooth loss was reported in 17 studies, however due to substantial heterogeneity in reporting of this outcome, nine studies could not be included in the meta-analyses (Axelsson and Lindhe, 1981c, Pihlstrom et al., 1984, Kaldahl et al., 1996a, Becker et al., 2001, Ramberg et al., 2001, Rosling et al., 2001, Serino et al., 2001a, Serino et al., 2001b, Loesche et al., 2002) and are described in a narrative form (Appendix I).

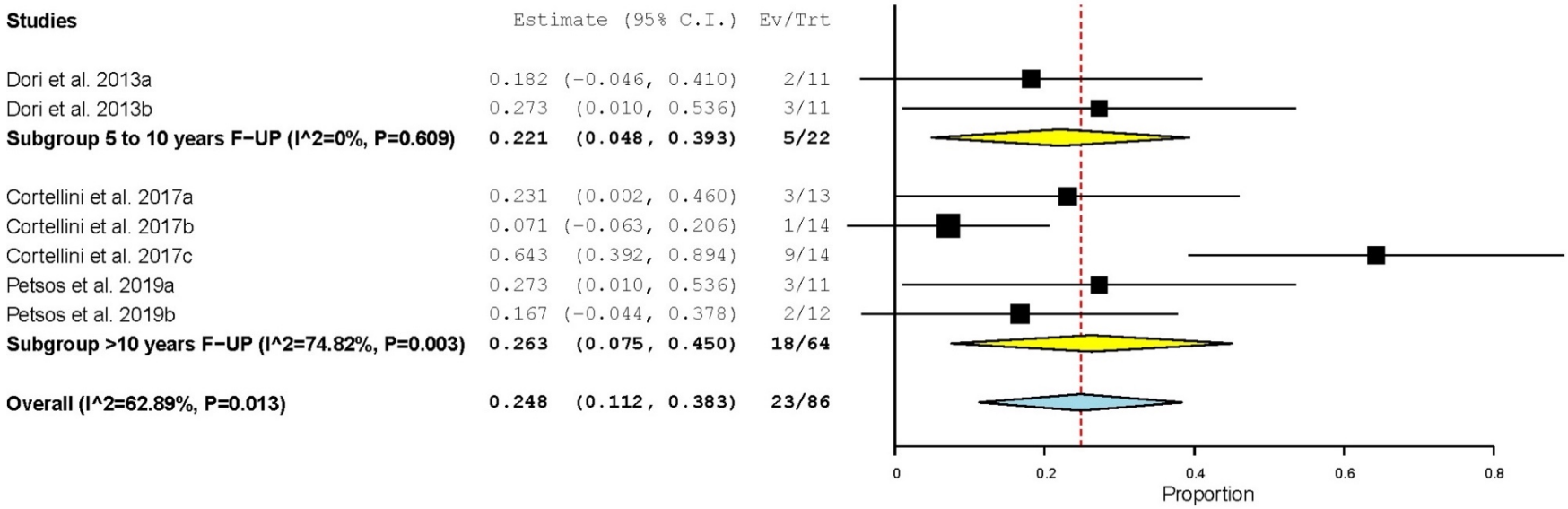
One study (Loesche et al., 2002) with regular 3 monthly SPC and a follow-up of a median of 61.2 months, reported the proportion of patients with tooth loss as being 56.8%. This is substantially higher than that estimated for the 3M subgroup analyses (8.0%, 95% CI 1.9-14.1%) and 5-10 FU subgroup (8.2%, 95% CI 3.0-13.4%). Additionally, the authors reported a substantial drop out rate of 46 participants from the original 90 subjects who entered the maintenance phase. On the other hand, one other small split-mouth study (Becker et al., 2001) reported the prevalence as 0% over the course of 5 years.

A number of studies reported mean tooth loss over the course of SPC (Axelsson and Lindhe, 1981c, Ramberg et al., 2001, Rosling et al., 2001, Serino et al., 2001a, Serino et al., 2001b). Some studies did not report the reasons for extraction and, so as to prevent under-estimation of tooth loss, were included in the summary.



F-UP = follow-up; C.I. = confidence interval; Ev = events; Trt = treatment group (i.e., total number of patients in the group)

Figure 38. Forest plot of proportion of patients with at least one site of clinical attachment loss ≥2 mm according to frequency of supportive periodontal care (SPC) - per protocol.



F-UP = follow-up; C.I. = confidence interval; Ev = events; Trt = treatment group (i.e., total number of patients in the group)

Figure 39. Forest plot of the proportion of patients with at least one site of clinical attachment loss ≥2 mm at patient level according to length of follow-up (per protocol).

(Appendix I). Other studies reported absolute numbers of teeth lost (Pihlstrom et al., 1984, Kaldahl et al., 1996a).

For studies with a 5-10 FU (Axelsson and Lindhe, 1981c, Pihlstrom et al., 1983, Pihlstrom et al., 1984, Kaldahl et al., 1996b, Becker et al., 2001, Serino et al., 2001a, Buchmann et al., 2002, Loesche et al., 2002, Loesche et al., 2005), average tooth loss per patient ranged from 0 - 2.6 teeth, whilst for studies with >10 FU (Ramberg et al., 2001, Rosling et al., 2001, Serino et al., 2001b), this ranged from 0.6 (±1.1) to 2.7 (±3.7) teeth per patient.

Studies which performed regular 3-4 monthly SPC (Axelsson and Lindhe, 1981c, Pihlstrom et al., 1983, Pihlstrom et al., 1984, Kaldahl et al., 1996b, Kaldahl et al., 1996a, Becker et al., 2001, Ramberg et al., 2001, Rosling et al., 2001, Serino et al., 2001a, Serino et al., 2001b, Loesche et al., 2002, Loesche et al., 2005) reported mean tooth loss ranging from 0 to 2.7 or absolute numbers of teeth lost (from the cohort) in the range of 8 - 46 (+2 roots) over the course of SPC.

FQ-2

One RCT (Bogren et al., 2008) and one prospective cohort (Costa et al., 2015) reported on tooth loss in patients previously treated for moderate to advanced periodontitis in SPC with unstable disease (Appendix J).

Bogren et al. (2008) compared locally delivered 8.8% doxycycline gel applications (every 3 months) with scaling and root planing (SRP) in 63 participants (test) in sites of PPD≥5 mm to SRP alone (control) in 65 participants. The study reported 25 lost sites due to tooth extraction (mean of 0.4 sites/participant) in the test group compared with 45 lost sites (mean 0.7 sites/ participant) in the control group over a 3-year follow-up period with routine 6 monthly SPC. The difference was not statistically significant ($p>0.05$) between treatment groups.

A prospective cohort study (Costa et al., 2015) analysed a population of 212 individuals over a 5-year period and retrospectively divided the cohort into two groups according to SPC visit compliance. 96 regular compliers (RC) and 116 IRREG compliers (IC) were subject to non-surgical therapy (NST) and, if deemed necessary, surgical therapy (ST) (if persistent PPD≥5 mm was detected). Mean tooth loss was reported to be 0.6 and 0.8 for RC and IC respectively. The difference was found to be statistically significant ($p<0.05$). Tooth loss was also assessed according to treatment modality within each compliance group. The RC group demonstrated a mean tooth loss of 0.3 (NST) and 0.8 (ST), compared with the IC group, which was 2.2 and 2.8 for NST and ST respectively. The differences between groups for both NST and ST were statistically significant. Interestingly, in both RC and IC groups, ST influenced greater tooth loss after 5 years.

Oral Health Related Quality of Life (OHRQoL)

No studies reported on OHRQoL (using validated tools) during long-term SPC. One study (Cortellini et al., 2020b) used the Italian translation of the Oral Health Impact Profile (OHIP)-14 questionnaire at baseline, 1, 5 and 10 years after treatment. One year after regenerative treatment (the first reassessment after APT), the mean OHIP-14 score was 6.6 (±2.4) and this was compared to a rehabilitated group (not relevant to this review). No data were reported beyond this.

Another study (Mendez et al., 2021), assessed OHRQoL based on the population of a previously published RCT (Angst et al., 2019) using the OHIP-14 questionnaire (validated for Brazil) at various time points in the 24 month study. The clinical study (Angst et al., 2019) compared two protocols of treatment, oral hygiene and oral prophylaxis (test) with additional subgingival instrumentation (control) during 3-monthly SPC visits. No statistically significant difference in severity ($p=0.311$), extent ($p=0.064$) or prevalence scores ($p=0.079$) were found between groups from baseline to 24-months. The

prevalence score favoured the control group at one time point (6 months) only (p=0.030). Using the anchor-based method, the study estimated the minimally important difference as 4.19, and overall, 33.9% (n=21) of participants showed a change greater than the minimally important difference. The authors reported that generally OHIP-14 scores remained low for both control and test groups over the 24-month period, thus concluded that both treatment protocols were able to maintain stability in OHRQoL.

Sites with CAL loss ≥2 mm

FQ-1

The majority of studies reported mean or median CAL over the duration of SPC. Some studies reported sites experiencing mean CAL loss≥2 mm as frequency distributions at various time points in SPC or in relation to initial PPD (prior to APT).

One study (Buchmann et al., 2002) of 13 participants reported the prevalence of disease progression over a 5-year follow-up at various time points. This study reported total of 64 sites which experienced disease progression and it was not clear whether these sites were recurrent or newly occurrent. The greatest number of sites experiencing disease progression occurred at 60 months, where 17 sites (18.3%) experienced CAL loss≥2 mm, followed by 12 sites (16.3%) which occurred at 36 months.

Another study (Kaldahl et al., 1996b) reported 'breakdown' sites where attachment loss was ≥3 mm. This group found a mean incidence per year of 1.24% over the course of 84 months of routine 3 monthly SPC. Of interest, a small proportion of participants (10%) accounted for a mean of more than 3.0% incidence per year, and these were all smokers.

Moder et al. (2012) conducted a split mouth study over 72 months of SPC and reported a total of 14 sites lost less than or equal to 2 mm of attachment. It

should be noted that some sites may have lost less than 2 mm of attachment, however, we were unable to extract this information.

Finally, one study with 64 participants with a follow up of 144 months in SPC reported mean annual proportions of sites showing 2 mm attachment loss with respect to baseline PPD (Table 2) (Ramberg et al., 2001). The greatest mean proportion was consistently seen in the PPD≥6 mm category for the SRP group which was 7.5% (±6.4) between 12 and 36 months, 7.8% (±8.7) from 36-60 months and 2.9% (±8.2) between 60 and 156 months of SPC.

FQ-2

Three studies reported on the sites with CAL loss≥2 mm (Jenkins et al., 2000, Tonetti et al., 2012, Angst et al., 2019) and all trials reported no statistically significant difference between test and control groups (Appendix J).

Angst et al. (2019) conducted a RCT which included 62 participants previously treated for moderate to severe periodontitis, over a follow-up period of 24 months. The study compared oral hygiene and oral prophylaxis (test) with additional subgingival instrumentation (control) during 3-monthly SPC visits. The authors highlighted that some participants entered SPC with residual pockets with bleeding on probing, thus periodontitis was not stable. The study found that mean PPD reduced significantly in both groups between BL and 24 months, and no statistically significant difference was noted between the test and control groups. The greatest proportion of CAL loss≥2 mm occurred with initial PPD=5 mm (24.6%), and 6mm (40.7%), when compared with initial PPD≤4 mm. Additionally, the mean number of sites PPD≥5 mm was assessed at 24 months. No statistically significant difference was observed between the test and control groups at 24-months.

One controlled clinical trial (CCT) (Jenkins et al., 2000) assessed 17 patients (146 sites) in a coronal scaling (CS) group versus 14 patients (130 sites) in a

subgingival scaling (SS) over a 12 month period. Participants who previously had been treated for periodontitis and entered SPC, presented with at least 4 pockets of PPD ≥4 mm. The appropriate intervention was delivered at baseline, 3, 6 and 9 months. The authors reported 21 of these 'loser' sites (defined as CAL loss≥2 mm) in each group, and no statistically difference between groups was found. Initial PPD ≥6 mm demonstrated a greater proportion of sites that were 'loser' sites, 28.6%, compared to 11.6% of those with initial PPD 4-5.9 mm for the SS group. The corresponding proportions for the CS group were 20.5% (initial PPD≥6 mm) and 11.8% (initial PPD 4-5.9mm). The authors concluded that the risk of attachment loss was greater if the initial PPD was 6mm or above, however this was only statistically significant for the SS group.

Tonetti et al. (2012) reported on 202 subjects in a multicentre RCT, comparing SRP and a single adjunctive 14% doxycycline gel application to SRP alone with a follow-up of 12 months. Participants had previously been treated for periodontitis and presented with at least four teeth with residual PPD ≥5 mm and a positive BOP. SPC was performed every 3 months for 1 year. A total of 15 participants (7.5%) experienced CAL loss≥2 mm (8 test, 7 controls). No statistically significant difference between groups were reported for any parameters at the 12 months.

Pockets of 5 mm or More with Bleeding on Probing

Only one study (Angst et al., 2019) reported on the number of sites ≥5 mm with bleeding on probing during SPC. The authors mentioned that some participants entered the study with residual probing depths (≥4 mm) and BOP, although the majority were resolved in APT. In the test group, the number of sites ≥5 mm at BL was 108 (2.8%), whilst in the control group, this was 58 (1.5%). The results of the study were reported according to initial PPD at BL (4mm, 5mm or ≥6 mm) and related both loss or gain of CAL≥2 mm to bleeding on probing at BL and ≥5 visits during the 24 months of SPC. For PPD≥5 mm, in the test group, 11 (68.8%) of sites which experienced CAL loss≥2 mm had BOP at BL, and this

was 3 (42.9%) for the control group. Regarding sites with BOP at ≥5 visits that experienced CAL loss ≥2 mm, the test group had 9 (56.3%) sites whilst the control group had 4 (57.1%). No statistically significant difference was observed between the groups.

Some studies reported on the proportion of BOP sites within specific PPD categories. Additionally, for treatment of recurrence in SPC, the mean number of sites with PPD≥5 mm was reported without mention of bleeding on probing (Bogren et al., 2008, Tonetti et al., 2012).

Reported Recurrent Sites

One study (Cortellini et al., 2017), reported recurrences that required retreatment. These recurrences occurred in all three treatment groups, MWF, modified papilla preservation technique (MPPT) with expanded-polytetrafluorethylene membrane (e-PTFE) and flap with e-PTFE. A total of 26 recurrences occurred in 20 years where sites of PPD≥5 mm at the 1-year reassessment, showed the highest frequency of recurrence that required re-intervention.

Kaldahl et al. (1996b) reported at total of 685 breakdown sites (461 from the SRP, Modified Widman Flap (MWF) and osseous recontouring groups) during the course of SPC that required re-treatment. From this, 5-12% of breakdown sites (experienced ≥3 mm attachment loss) which were subsequently re-treated, experienced further loss of attachment.

Sites That Need/ Experience Retreatment

Eleven prospective studies reported on methods to treat recurrence during SPC (Jenkins et al., 2000, Bogren et al., 2008, Lulic et al., 2009, Tonetti et al., 2012, Costa et al., 2015, Killeen et al., 2018, Angst et al., 2019, Jasa et al., 2020, Mendez et al., 2021, Andere et al., 2022, Killeen et al., 2022) with at least 12 months follow up. A variety of treatments were used to treat recurrences,

including supra- and subgingival debridement, photodynamic therapy and adjunctive application of doxycycline (with NST), simvastatin (with surgical therapy), minocycline microspheres (with NST), or enamel matrix derivatives (with surgical therapy). Two recent RCTs (Andere et al., 2022, Killeen et al., 2022) found a statistically significant between test and control treatments at the 12 months follow up.

Andere et al. (2022) treated adult patients (<35 years old) initially diagnosed with Stage III or IV, grade C periodontitis who were in an SPC programme and had experienced recurrent disease (PPD ≥5 mm and CAL ≥5 mm with BOP). This 12-month RCT (n=46) compared open flap debridement (modified papilla preservation flap), with NST and five applications of photodynamic therapy (PDT) at days 0,1,2, 7 and 14. The authors found that the OFD group (control) had a statistically significant greater PPD reduction (p=0.001) compared to the PDT group (not CAL gain), however, this was at the expense of greater dentine sensitivity (p=0.03) and post-operative pain (p=0.03) at 7 days.

One other university-based study (Killeen et al., 2022) treated recurrent sites (6-9 mm PPD) in patients previously treated for Stage III Grade B periodontitis. The RCT compared surgical papilla reflection, NST, Simvastatin and methylcellulose (test) with surgical papilla reflection, NST and methylcellulose alone (control). At 12 months, the test group displayed statistically significant greater PPD reduction (p=0.007) and CAL gain (p=0.03) when compared with the control group.

Health Economic Outcomes

Two studies (Cortellini et al., 2017, Cortellini et al., 2020b) reported total cumulative costs for operative interventions. This cost calculation included actual cost of the procedures (using average fees from nine practices in Italy), all complications experienced which required re-treatment, and included tooth loss. Cortellini et al. (2020b) reported (in graphical form) that the cumulative

costs for a regenerative procedure over 10 years, amounted to a mean of just over €2500, however SPC appointments were not included in this calculation. The cumulative costs over a 20-year period (including 3 monthly SPC) ranged from a mean of €3090.98 (±210.66) to €3382 (±88.95), depending on the initial surgical therapy (Cortellini et al., 2017).

Other Patient Reported Outcomes (PRO)

One study (Kaldahl et al., 1996a) reported on the occurrence of periodontal abscesses in the context of the therapy type in APT, over the 84-month follow-up. Twenty-seven abscesses were reported, with 23 episodes (85%) occurring in the group originally treated by coronal scaling alone. Deep probing depths (≥7 mm) at the initial examination was associated with 17 abscesses (63%).

Masticatory function and aesthetics were assessed by Cortellini and co-workers (Cortellini et al., 2020b). A 5-point Likert scale was utilised to assess changes from baseline to 10 years. The authors report that between the one and ten-year follow-up period, the proportion of participants with 'no concern' in regard to masticatory function remained stable. Those reporting, 'some concern' appears to increase over the 9 years of SPC (graphical information available only). A similar scale was used for assessing aesthetics, and once again, whilst those reporting 'no concern' appears to remain stable between the one and ten-year follow-up, those reporting 'some concern' appears to increase over the follow-up.

Two studies reported on adverse events in the context of experimental treatment groups (Jenkins et al., 2000, Tonetti et al., 2012). Jenkins et al. (2000) reported no adverse events in relation to coronal and subgingival scaling. In contrast, Tonetti et al. (2012) reported that as 12 months 49 patients (75 adverse events) in the control group and 34 patients (56 adverse events) in the test group. The authors reported no difference in the incidence of adverse

events was observed between the groups (a test of significance was not carried out).

One study (Andere et al., 2022) comparing treatments for recurrence in SPC, evaluated patient-centred outcomes following OFD or PDT using visual analogue scales. The authors found that although the clinical outcome of PPD reduction was statistically significant greater for the OFD group, PDT participants had less dentine sensitivity at 15 days (p=0.03), less post-operative pain at 7 days (p=0.03) and fewer took analgesics at 7 days (p=0.03).

7.4.6 Risk of Bias

FQ-1

All studies were assessed as prospective cohorts (SPC being the exposure) using the modified version of the NOS. Overall, most studies had a low risk of bias (Appendix K) assessed as having five out of a possible six stars in regard to the selection and outcome domains. Two studies were found to have a moderate risk of bias, with four stars (Hou et al., 1997, Loesche et al., 2002), with one of these studies having a low score in the exposure/ outcome domain (Hou et al., 1997). When assessed by means according to domains of the NOS, it was found that 'selection' had an average score of 2.9 (SD ± 0.3), whilst the 'outcome/ exposure domain' showed an average 2.5 (SD ± 0.6).

FQ-2

Nine RCTs were assessed using the Cochrane Risk of Bias Tool 2.0 (Appendix L). One study (Andere et al., 2022) was judged as having a 'low' risk of bias, six studies of, 'some concern' (Bogren et al., 2008, Lulic et al., 2009, Tonetti et al., 2012, Angst et al., 2019, Jasa et al., 2020, Mendez et al., 2021), and two studies was deemed to be, 'high' risk (Killeen et al., 2018, Killeen et al., 2022).

The Robins-I tool was used to assess the quality of one interventional non-randomised controlled trial (Jenkins et al., 2000) and one prospective cohort (Costa et al., 2015). Both studies were judged to be of 'serious' overall risk of bias (Appendix M).

7.5 Discussion

7.5.1 Key Findings

No studies could inform on OHRQoL during long-term SPC, however OHRQoL might be maintained with regular SPC visits regardless of treatment modality (non-surgical) employed to address disease progression.

Findings of the meta-analyses indicated that the proportion of patients who experienced tooth loss was 9.6% (95% CI 5-14%) i.e., 10% of patients can expect to lose at least one tooth during SPC of at least 5 years duration. Subgroup analysis showed that the proportion of patients with regular 3 monthly SPC recall visits who experienced tooth loss was 8.0% (95% CI 2-14%), compared with 11.9% (95% CI 5-19%) for the IRREG SPC group (p=0.161). A shorter length of follow-up (5-10 years) corresponded to an average of 8.2% (95% CI 3-13%), and as this time period increased (>10 years), the proportion also increased to 12.7% (95% CI 4-22%). Studies which could not be included in the meta-analyses reported a mean tooth loss per patient of 0-2.7 (±3.7), which was not greatly affected by the length of follow-up in SPC.

Patients who experienced at least one site of CAL loss≥2 mm was estimated to be 24.8% (95% CI 11-38%) i.e., 25% of patients can expect to have at least one site with progression of periodontitis by at least 2 mm during SPC of at least 5 years duration. According to the subgroup analyses, more patients who underwent 3 monthly SPC experienced CAL loss≥2 mm, which amounted to 30.2% (95% CI -2 – 63%), whilst the proportion of those in IRREG group SPC was 21.4% (95% CI 10-33%). The longer length of follow up of >10 years, led

to a slightly higher proportion of patients with attachment loss of 26.3% (95% CI 8-45%) as compared to 22.1% (95% CI 5-39%) for the 5-10 yr group.

Limited weak evidence suggests (based on one study, n=46) that periodontal surgery (OFD) may be more effective in the treatment of residual pockets than NST with regard to PPD reduction at 12M.

7.5.2 Agreements and Disagreements with Other Reviews

This is the first systematic review assessing disease progression with the primary outcome of tooth loss, in the phase of SPC in the long term (> 5years). The results of my review agree with a recent Cochrane review (Manresa et al., 2018) which reported on RCTs with a minimum of 12 months follow-up to determine the effects of maintenance care in the management of periodontitis. The authors found the quality of evidence to be low or very low and could not make conclusions on the merit of SPC versus monitoring alone/irregular SPC. Furthermore, no conclusion could be drawn regarding the optimum frequency of SPC.

One recent systematic review (Sanz-Martin et al., 2019) similar to the present review, reported mean CAL loss ranging from ≤0.5 mm to >1 mm and proportion of sites showing CAL loss≥ 2mm ranging from 3-20% in their qualitative review. We were unable to compare the outcomes, as reporting of CAL loss in the current review was different and on a patient level. Tooth loss was reported at 1% based on one study only. One explanation for the differing results could be that Sanz-Martin et al. (2019) excluded regeneration studies, which formed a key part of the current review. Additionally, the present review only included studies with minimum 5 years specifically in the phase of SPC, rather than 5 years follow-up (which was often calculated before APT). Quality assessment also differed. The present review employed the modified version of the NOS to assess the SPC phase only, whereas the previous authors assessed studies based on the APT phase (thereby using the Cochrane

collaboration tool for RCT and NOS for prospective cohorts). Their judgement was thus that most studies were at a high risk of bias, compared with this review which found that most studies were at low risk of bias.

Overall Completeness and Applicability of the Evidence

This review intended to focus on patients diagnosed with stage IV periodontitis, however, the majority of studies were published prior to the most recent classification, with the exception of one (Cortellini et al., 2020b) whereby the authors retrospectively classified patients as stage III-IV. No data could be extracted on what would specifically be considered stage IV periodontitis. In light of the fact that we have a lack of data on complexity factors such as numbers of teeth previously lost to periodontitis, masticatory dysfunction, bite collapse and/ or remaining teeth, it would be reasonable to assume that the majority of studies in this review probably represent stage III periodontitis patients. It is unclear to what extent complexity factors might influence disease recurrence in SPC, and thus my results might be generalised to include stage IV cases.

The limited number of studies included in this systematic review might seem surprising, however prospective long-term studies (> 5 years) in the periodontal literature are rare, with majority having a clear focus on the outcomes of APT with ≤12 months follow-up.

It is unclear if the data presented are representative of disease occurrence, recurrence or progression, furthermore, there was a lack of information whether tooth loss was due to periodontitis alone. A number of studies did not present any information on reasons for tooth loss, thus the results presented in this review could be over-estimated. Although my subgroup analysis, showed that the proportion of patients who experienced CAL loss≥2 mm was greater for those in the 3M subgroup than the IRREG SPC subgroup, this difference was not statistically significant. Additionally, the disparity may be explained by a

single outlier (Cortellini et al., 2017) whereby participants in this group presented with a greater number of residual PPD at the start of SPC and subsequently greater disease recurrence.

The studies in this systematic review were largely conducted in the university setting, with only a few conducted in private practice, some of which were from the same practice. Additionally, the meta-analyses included studies whereby regenerative procedures were part of APT, which limits the applicability of the evidence to all periodontal patients in general practice. The variability of SPC recall intervals and possible variety of operators, however, may be more realistic of that which occurs in practice. This systematic review was also unable to inform on specialist versus non-specialist SPC in regard to disease progression/recurrence. A previous systematic review (Gaunt et al., 2008b) reported that SPC delivered in specialist care represented a greater financial cost, but this was accompanied by greater periodontal stability (CAL) over a minimum follow-up period of 12 months.

There was an obvious lack of detail regarding the description of SPC and the majority of studies provided no information on whom carried out the recall appointments. Use of the CONSORT – NPS extension (Leow et al., 2016) might help guide authors to describe the SPC intervention more completely even for non-randomised trials.

Studies which included PRO and health economic data were clearly lacking, therefore no conclusions could be made on the impact of disease recurrence in regard to these important outcomes from this review. However, health economic modelling of SPC has demonstrated that it is cost-effective in developed economies when considering tooth loss or progression of CAL (Pennington et al., 2011). Furthermore, prevention of tooth loss in an aging population is a priority for long-term health and wellbeing (Tonetti et al., 2017a). In relation to oral health-related quality of life (OHRQoL) a recent retrospective pilot study showed that after up to 32 years of individualised intervals of SPC, OHRQoL

impacts were low (Graetz et al., 2020). Interestingly, there were higher OHRQoL impacts associated with 'insufficient' adherence to SPC (defined as SPC interval extending more than half of the recommended interval) compared with those with 'sufficient' adherence (maximum of ±6 months of recommended interval) (Graetz et al., 2020), which is in agreement with a previously published retrospective study (Sonnenschein et al., 2018).

Six studies specifically investigated treatment of recurrence in SPC, with only four being RCTs. Due to heterogeneity in terms of methodology and outcome reporting we were unable to answer FQ-2. However, two RCTs (one of low risk of bias and one of high risk of bias) found surgical intervention (OFD) alone (Andere et al., 2022) or with adjuncts (Simvastatin gel) (Killeen et al., 2022)was promising with regard to PPD reduction and CAL gain, however, this must be balanced with short-term discomfort of dentine hypersensitivity and pain. Some of the included studies that addressed FQ-1 indicated that management of recurrence was left to the discretion of the operators, but usually were managed by further subgingival debridement. Success of this treatment modality in regard to resolution or halting progression of disease was not reported, although one study mentioned that 'most' recurrent sites responded favourably to NST (Costa et al., 2015).

Overall Quality, Strength and Consistency of the Evidence

The quality assessment judged the majority of included studies had a low risk of bias in regard to the SPC phase (FQ-1), with two studies found as having moderate risk. The meta-analysis highlighted heterogeneity for both tooth loss and CAL loss≥2 mm, which reflects the limited number of studies fulfilling the inclusion criteria for this systematic review. Type of initial therapy (regenerative or non-regenerative) was one factor that could explain some heterogeneity, however residual unexplained heterogeneity should be assumed, and results should be interpreted with caution. Studies included in the meta-analysis were predominantly of a regenerative nature. Split mouth studies were included in

this review, and it should be acknowledged that there is an uncertain risk of contamination from one side/ quadrant to another. This, however, would be most relevant for studies assessing APT. The strength of the evidence to answer FQ-2 was weak, with two studies having a 'serious' risk of bias (Robins-I tool), three studies of, 'some concern' and one study determined as having a 'high' risk of bias (Cochrane Risk of Bias Tool 2.0). There was no clarity on which treatment modality (if any) was superior in the management of disease recurrence/ progression in SPC.

Finally, it should be recognised that studies included in this review were not originally designed for assessment of disease progression/recurrence and/or treatment of recurrence in SPC, thus the strength of conclusions from these studies is weak.

7.5.3 Strengths and Limitations of the Review

In order to minimise the risk of bias in the review process, this protocol was submitted *a priori* to PROSPERO. Furthermore, screening, study eligibility, data abstraction and quality assessment were all conducted in duplicate and independently.

This systematic review is the first to comprehensively look at disease progression/ recurrence in SPC, incorporating all forms of treatment in APT, over a minimum of 5 years in maintenance. Additionally, it is the first to assess methods of managing disease progression/ recurrence of patients in an established SPC programme. We incorporated a sensitive search strategy in multiple electronic databases in order to detect a broad range of studies. Other strengths were the quality assurance including duplicate, independent study screening and data extraction.

A number of studies described a significant number of drop-outs over the follow up period, and in order not to underestimate the prevalence of tooth loss and

CAL loss≥2 mm we chose to carry out a per protocol meta-analyses, however for comparison and thoroughness, an ITT analysis was also included for tooth loss.

A number of limitations could be identified which might bias the outcomes of this systematic review. Publication bias is an important problem in evidence-based Medicine, and this may lead to selection bias in systematic reviews. In the present review, some publications following the screening of titles and abstracts could not be obtained in full-text and clarification on studies from authors could not be followed up. We were also limited to publications in the English language, which means that relevant studies could have been missed.

Some post-hoc changes were made to the original protocol. We added case-series to the exclusion criteria, and a distinction was also made as to what we defined as a case-series versus prospective cohort. Additionally, a modified version of the NOS needed to be implemented to adjust for the studies included in the review. One post-hoc analysis was included based on the data collected. This was subgrouping according to SPC recall intervals and was conducted as it became clear that a number of studies had quite variable or unmonitored SPC visits.

7.5.4 Implications for Practice and Policy

Most patients enrolled in SPC following successful treatment of periodontitis should not expect to experience tooth loss, which, considering the severity of disease (stage III or IV periodontitis) is highly encouraging. However, 25% of patients are likely to experience further CAL loss. It is unclear from the data whether the CAL loss represents periodontitis progression or gingival recession in shallow pockets. However, in some studies (Bogren et al., 2008, Costa et al., 2015, Cortellini et al., 2017), CAL loss was noted as an increase in PPD at some sites, suggesting disease progression. These findings, together with

other evidence discussed in this review, highlight that SPC is an important element in the long-term management of stage III and IV periodontitis.

Evidence external to this review indicates that SPC is cost-effective in developed economies (Pennington et al., 2011, Schwendicke et al., 2020)and that prevention of tooth loss is important in ageing populations (Tonetti et al., 2017a).

Although SPC is poorly described in the literature, the common elements in studies suggest that it should include repeated; risk assessment, health behaviour motivation, tailored oral hygiene coaching, professional mechanical plaque removal and targeted subgingival debridement appropriate for each patient (Rosling et al., 2001). The recently published 'Clinical Practice Guideline' from the recent European Federation of Periodontology (Sanz et al., 2020) supports inclusion of these elements also. Individual needs of each patient should be considered when deciding on the frequency of SPC, and, until the influence of risk factors is better understood, this is likely to be no longer than 3-6 monthly for stage III-IV periodontitis patients. Whilst there was no evidence of a difference in tooth loss between groups receiving 3 monthly and less regular SPC, it is important to remember that these were not randomised controlled trials and were therefore at higher risk of bias. A lack of randomised evidence was also found in another systematic review (Manresa et al., 2018).

7.5.5 Implications for Further Research

There is a clear need for high quality trials focussed on SPC, with particular emphasis on including OHRQoL, decision-making on SPC recall intervals, and documenting and treating disease progression/ recurrence.

Patient-reported outcomes in long-term SPC should be a priority in future research, as the potential to include meaningful and relevant outcomes (beyond

clinical outcomes) to patients themselves has the potential to motivate and reduce health inequalities by increasing health literacy.

SPC should be carefully described in detail including who delivered it and the components of care using the CONSORT-NPE as a guide, even for non-randomised studies. The demographics of the population entering SPC should be clearly described, particularly with reference to risk factors of smoking and diabetes. Information on tailoring procedures in each SPC visit and recall intervals would be highly valued.

In order to increase the clinical relevance of studies, it would be ideal to report outcomes such as tooth loss or CAL loss at a patient level, in addition to mean values.

7.6 Conclusions

Within the limitations of this study, we have found that the mean prevalence of tooth loss in patients in SPC for 5 years or more is less than 10% of patients, with a tendency for greater prevalence with time. Regular SPC appointments (3 monthly) appears to be important for reduction of the prevalence of tooth loss.

8. OVERALL DISCUSSION

The chapters presented in this thesis outline four pieces of research which document OHRQoL with respect to important components of a patient's journey in the management of severe periodontitis.

Chapters 1, 2 and 3 of this thesis presented rationale, background and research questions designed to answer gaps in the current knowledge. The first two research hypotheses addressed modalities of treatment; i)'non-surgical periodontal therapy in the treatment of stage III/IV periodontitis is associated with an improvement in OHRQoL and QoL', and ii) '[redacted] The third research hypothesis addressed treatment in patients with a co-morbidity, 'Comprehensive periodontal therapy (non-surgical therapy and surgical therapy, if required) in patients with type 2 diabetes is associated with an improvement in OHRQoL'. Finally, the last study hypothesis addressed patients in long-term periodontal maintenance, and stated, 'Long term, regular SPC is associated with an improvement in OHRQoL and maintains the stability of periodontitis'.

The chapters following (4, 5, 6 and 7), detailed the research carried out to test the research hypotheses above, and answer specific research questions (see Chapter three). The results of these studies have contributed to the existing knowledge base on OHRQoL in patients with severe periodontitis and this final chapter will present a summary of key findings and further discussion on how these studies may influence future research on OHRQoL in periodontology.

8.1 Key Findings

This thesis presented research conducted with respect to OHRQoL and a variety of treatment modalities in the treatment of periodontitis, including patients with and without co-morbidities (diabetes). Additionally, research

investigating OHRQoL when patients have entered long-term periodontal maintenance programmes is presented. The key findings of Chapters 4, 5, 6 and 7 are presented below in the context of the eight initial research questions.

A summary of the findings with respect to OHRQoL and QoL for each study is found in Table 39.

Table 39. Summary of OHRQoL and QoL key findings.

Study	PROM (Follow Up)	Key Findings
Ch 4. Triangulation of NST, OHRQoL and QoL	OIDP CS-OIDP EQ-5D-5L EQ-5D-VAS (6-8 weeks)	• NST improved OHRQoL (CS-OIDP). • QoL (EQ-5D-5L and EQ-5D-VAS) did not change following NST. • OHRQoL was weakly correlated with QoL, but not with extent of disease (PPD≥5 mm).
[redacted]	[redacted]	• [redacted]
Ch. 6 PROMs in patients with Diabetes and Periodontitis	CS-OIDP (12 months)	• Periodontal therapy improved OHRQoL (CS-OIDP), irrespective of therapy. • OHRQoL was not statistically significant correlated with diabetic control (HbA1c). • Self-rated periodontal health correlated with self-rated QoL irrespective of treatment approach.

The minimally important differences and effect sizes for each interventional study is summarised in Table 40.

Table 40. Summary of minimally important difference and effect sizes.

Study	MID		Effect Size	Proportion of participants ≥ MID (n)
Ch 4. Triangulation of NST, OHRQoL and QoL	OIDP	4.70	0.16	17% (15)
	CS-OIDP	4.58	0.24	16% (14)
[redacted]	[redacted]			
	[redacted]			
Ch. 6 PROMs in patients with Diabetes and Periodontitis	CS-OIDP	5.32	0.29	30% (74)

8.1.1 Triangulating OHRQoL, QoL and clinical outcomes following non-surgical therapy

The first and second research questions were, 'what is the impact of NST on both OHRQoL and QoL?' and 'what is the relationship between OHRQoL and QoL following NST?'

The aim of the prospective case series presented in Chapter 4 was to assess the relationship between OHRQoL, QoL and clinical following NST in patients with Stage III and IV periodontitis.

The results of this interventional study which recruited 100 stage III/ IV periodontitis patients confirmed the findings of previous studies with regard to OHRQoL, such that NST results in improvement in the short term (minimum of 6-8 weeks following therapy), however QoL did not significantly improve. The lack of change in QoL may be due to a lack of sensitivity of the PROM (EQ-5D-3L) to periodontal outcomes (National Institute for Health and Care Excellence, 2022a). One epidemiological study suggests (Brennan et al., 2007) the EQ-5D-3L questionnaire can detect impacts in patients with periodontitis, however did not evaluate responsiveness following an intervention. In a random sample of 709 participants in Australia, Brennan et al. (2007) assessed both clinical status and HRQoL using the EQ-5D-3L questionnaire. The authors found that 25.8% of people who had a PPD ≥6 mm (n=31), had an impact in the pain/ discomfort dimension 49.4% of the time, and concluded its potential use (in combination with a condition specific OHRQoL measure) in future studies, particularly for calculating health utilities and economics.

In line with the improvement in OHRQoL utilising the OIDP questionnaire, self-rated dental and periodontal health (global self-ratings) also improved significantly following NST.

Triangulation of clinical outcomes with OHRQoL and QoL highlighted that OHRQoL and QoL demonstrated a negative weak statistically significant correlation at BL and reassessment, meaning that worse OHRQoL correlated with worse QoL. However, neither OHRQoL or QoL were correlated with extent of disease (as measured by number of PPD≥5 mm).

An estimation of the MID for OIDP was 4.70 and for CS-OIDP was 4.58. Less than 20% of participants experienced a change in OIDP and CS-OIDP scores above the MID. The proportion of participants receiving a benefit greater than or equal to the MID appears low, particularly considering that over 95% (n=84) of respondents felt their periodontal health either improved a little or a lot after treatment. Tsakos et al. (2010) reported that 'slightly more than one-third' of the participants in their study experienced changes in OHRQoL larger than the MID, which, although there was a greater proportion of participants than my study, it is still lower than what might be expected. This finding may be in part due to the inherently statistical nature of the distribution-based approach of calculating MID, which estimates according to dispersion of the data and results in a moderate to large effect size (excluding small effect sizes). Furthermore, it may be that the PROM instrument (OIDP) is not sufficiently responsive to change following a periodontal intervention (Lin et al., 2009).

The estimate of the proportion of participants (Chapters 4-6) reaching a change in score equivalent to or greater than the MID (beyond measurement error) appears to be a unique element when reporting PROMs across the dental and medical literature. A search of clinical studies evaluating HRQoL changes in the treatment of chronic conditions, found a limited number of studies (in medicine only) presenting data in this way. One retrospective analysis (Liu et al., 2014) compared HRQoL with reference to three PROMs (Oswestry disability index, short-form 36 and Scoliosis Research Society-22 questionnaires), , evaluating surgical (operative) interventions to non-operative interventions in the adult spinal deformity. The authors found the proportion of patients

reaching the MID varied according to the PROM and intervention, with the range in the operative group (n=239) being from 43% to 74% and the non-operative group (n=225) being from 7% to 24%. The results from my studies appear to be in line with the non-operative group, however it also must be considered that in contrast to many cases with periodontitis, pain is a significant factor in chronic hip conditions which often leads to seeking an intervention. Presumably, surgical intervention results in a significant reduction in the pain and functional domains, which, in the case of the treatment of periodontitis is less often the case when considering surgical intervention(s). Chen et al. (2016) found that 33.8% of Taiwanese stroke patients (n=65) reached the threshold of the MID 3-4 weeks following a rehabilitation therapy using the EuroQoL questionnaire, a finding which is similar to that of my study (chapter 6) on patients with diabetes.

Another retrospective cohort study (Silverstein et al., 2016) evaluated HRQoL (EuroQoL, Pain Disability and Patient Health Questionnaires) in 212 patients who underwent lumbar decompression due to chronic pain in patients with (n=30) and without diabetes, with a minimum follow-up of 6 months. The authors found that 55% of non-diabetics achieved the threshold MID in the EuroQoL questionnaire, compared with 23% of the patients with diabetes ($p<0.01$), which may imply that having a co-morbidity such as diabetes may impact on the size of benefit following an intervention. Considering the relatively small number of participants with diabetes in this retrospective study, conclusions should be treated with caution. In contrast, my study (chapter 6) found that approximately 30% (n=74) of participants reached the threshold MID, whilst less patients without diabetes (chapters 4 and 5), reached the threshold (range: 16% - 20%).

As is the case with MID, due to the variety and severity of conditions, interventions and tools used to measure HRQoL, it is difficult and perhaps inappropriate to compare the proportion of participants reaching the threshold of

MID from my study with others in the medical literature. Perhaps of greater benefit would be to compare the proportion of participants reaching the threshold MID between intervention arms, in order to evaluate better the relative effects of contrasting treatments.

[redacted]

[redacted]

8.1.3 Impact of periodontal treatment on PROMs in patients with diabetes

The fifth research question was, ‘ in patients with periodontitis and diabetes, does comprehensive periodontal therapy impact on OHRQoL?

The aim of the RCT presented in Chapter 6 was to assess the impact of periodontal treatment on OHRQoL in patients with type 2 diabetes over 12 months of follow-up.

This 12 month RCT recruited 264 participants and showed that OHRQoL significantly improves in patients living with diabetes following periodontal therapy, regardless of treatment intensity. A statistically significant improvement in HbA1c was also demonstrated following intensive periodontal therapy (NST and ST therapy), however was not significantly correlated with OHRQoL.

The most frequently reported dimensions negatively affected by the participants at baseline were the ability to eat, ability to clean their teeth, relaxing and smiling. Following therapy (regardless of intervention), the greatest improvement reported was in the ability to clean their teeth.

The results of Chapter 4, 5 and 6 provide evidence that NST and ST improves OHRQoL in patients treated for stage III and IV periodontitis and improves OHRQoL in patients with periodontitis living with diabetes.

A MID for CS-OIDP was estimated at 5.32 using the distribution-based approach, with a small to moderate effect size of 0.29. Approximately 30% of participants experienced a change in score greater than or equal to the MID.

8.1.4 Supportive periodontal care regarding clinical and PROMs

The sixth, seventh and eight research questions were, 'what impact does regular long-term SPC have on OHRQoL and QoL when compared with irregular/ no SPC?', 'what is the prevalence of tooth loss in periodontitis patients enrolled in a long term SPC programme?' and 'what is the prevalence of disease progression (as measured by CAL loss) in periodontitis patients enrolled in a long term SPC programme?'

The aim of the systematic review and meta-analysis presented in Chapter 7 was to assess the impact of long-term SPC on OHRQoL and QoL, and to determine the prevalence of tooth loss, disease progression when compared with no/irregular SPC. A further aim was to determine effective treatment modalities to address disease recurrence/ progression.

Overall, the systematic review found that regular (3 monthly) SPC afforded benefits in the long-term, compared with no or irregular SPC, when assessing the proportion of patients who experience tooth loss, and regular SPC appears effective in maintaining disease stability.

24 studies were included to inform on tooth loss and disease progression, whilst 11 studies were included to inform on the treatment of disease recurrence/ progression. All included studies were assessed for OHRQoL, QoL and any patient-based outcomes. Eight of the included studies were included in the

meta-analysis, and the others were qualitatively described due to heterogeneity in methodology and outcome measures.

The systematic review found no studies to inform on OHRQoL during long-term SPC, however OHRQoL may be maintained with regular SPC visits (regardless of treatment modality) employed to address disease progression.

The meta-analysis found that the proportion of patients who experienced tooth loss was 9.6% (95% CI 5-14%) i.e., 10% of patients can expect to lose at least one tooth during SPC of at least 5 years duration. Regular 3 monthly SPC resulted in a smaller proportion of patients who experience tooth loss (8%, 95% CI 2-14%) when compared with irregular SPC (11.9%, 95% CI 5-19%).

In contrast to tooth loss, a greater proportion of patients is expected to experience at least one site of CAL loss≥2 mm (24.8%, 95% CI 11-38%) during SPC of at least 5 years duration. According to the subgroup analysis, more patients who underwent regular 3 monthly SPC appointments experienced CAL loss≥2 mm (30.2%, CI -2 - 63%) when compared with irregular SPC (21.4%, 95% CI 10-33%).

Limited weak evidence suggests (based on one study, n=46) that periodontal surgery (OFD) may be more effective in the treatment of residual pockets when compared with NST in terms of PPD reduction at 12M.

8.2 Strengths of this Research

Several strengths exist for this body of research, which makes the results particularly useful in designing future studies on the topic.

8.2.1 OHRQoL, QoL and Clinical Outcomes

The prospective case series presented in Chapter 4 was the first to triangulate OHRQoL, QoL and clinical outcomes in stage III/ IV periodontitis patients. The incorporation of a QoL measure in the treatment of periodontitis was a

particularly unique feature, not seen in other trials. Additionally, multiple operators of varying experience and time-frames of administering the PROMs at baseline and 6-8 weeks following NST, might be more representative of everyday specialist practice.

An important strength of the design of this thesis, is the inclusion of populations with and without a significant co-morbidity (diabetes), to evaluate the impact of periodontal treatment(s) in the context of potentially debilitating conditions.

8.2.2 Estimation of Minimally Important Difference

A feature of this thesis is the estimation of a MID for three different patient populations, experiencing a number of treatment interventions utilising the distribution-based approach. Although the calculation of MID is strongly recommended in QoL research to determine level of change meaningful to the patient, it has rarely been published in periodontal research. Therefore, the results of this thesis can help to estimate more accurately MID in different populations.

8.2.3 OHRQoL and SPC

The rigorously conducted systematic review presented in Chapter 7 was the first to evaluate OHRQoL in combination with clinical outcomes of tooth loss and disease progression in long-term SPC. Although no studies were found utilising validated PROMs, it provides evidence that research is urgently needed on this topic.

Finally, the research presented in this thesis is aligned with the call for action (over 20 years ago) to include PROMs in periodontal research (Heitz-Mayfield et al., 2002, Lindhe and Palmer, 2002) and remains a key research priority today (Sanz et al., 2020, Herrera et al., 2022).

8.3 Limitations of this Research

The results of this research can be used as a basis for future studies; however, a number of limitations should be acknowledged.

8.3.1 Interventions

This PhD could not explore all possible interventions (or combinations of such) which are involved with the treatment of periodontitis. The most common therapeutic interventions of NST and ST were explored, however different protocols (i.e., quadrants versus full mouth debridement and/or adjuncts to therapy) were beyond the scope of this thesis. Furthermore, ST is a broad intervention with varying approaches which may involve multiple teeth or sites, and levels of invasiveness (e.g., soft tissue and/or bone removal) and the extent to which these elements impact on OHRQoL was not explored.

8.3.2 Participants and Generalisability

The participants in the clinical studies presented in this thesis were diagnosed with stage III or stage IV periodontitis, however we did not differentiate between the stages. We were therefore unable to make any conclusions on whether a more advanced stage of periodontitis exhibited a greater or worse impact on OHRQoL following NST or ST. Additionally, complexity factors (e.g., including those that are used to differentiate between stage III and IV periodontitis) could also affect OHRQoL change following treatment, and these were not considered in this thesis.

This PhD was only able to focus on an adult population without significant co-morbidities (Chapters 4 and 5) or with a single co-morbidity, diabetes mellitus (Chapter 6). Other co-morbidities (including multiple co-morbidities) may have an important impact on PROMs following therapy which ideally should be explored in future research. Additionally, impacts of therapy on children and adolescents were not explored in this thesis.

The participants in all three clinical trials (Chapters 4, 5 and 6) included stage III/IV periodontitis patients, therefore the resultant improvement in OHRQoL may not be extrapolated to populations with milder forms of the disease. Furthermore, the estimations of MID may not be appropriate for all applications in the treatment of periodontitis, as it may vary according to the population and context (Revicki et al., 2006).

8.3.3 Setting and Operators

The clinical studies were all set in either a hospital setting (Eastman Dental Hospital, London, United Kingdom) or the Eastman Clinical Investigation Centre (ECIC), a dedicated research facility. It is therefore difficult to extrapolate these results to a different setting such as an extra-mural clinic or private practice. Furthermore, the operators carrying out the interventions in both randomised controlled trials were experienced periodontists, therefore the results may not be generalised to interventions carried out by general dental practitioners.

The clinical study presented in chapter 4 involved operators training to be periodontal specialists (supervised by specialists) with varying degrees of experience. No limitations were set for number of appointments, length of appointments nor instruments used. Whilst this may be seen as a limitation due to the lack of standardisation of procedures and operators, it also may be a more genuine representation of the patient's journey both in public and private settings.

8.3.4 PROMs

Presently, there is no 'gold standard' PROM questionnaire (or combination of such) for use in periodontal research, thus the choice of the OIDP and EQ-5D questionnaires was principally determined by familiarity by the research team. A number of limitations exist for the OIDP questionnaire which includes 'floor' and 'ceiling' effects. These effects occur when many participants have a minimum/ low score or maximum/ high score respectively, thus the questionnaire is unable to discriminate between individuals at extremes of the scale and information could be lost. Whilst the OIDP is able to produce a condition-specific score, we were unable to determine further, which aspects of that condition might have the greatest impact. For example, a participant attributing an impact to periodontitis must tick a box which includes 'loose tooth, bleeding gums, receding gums, tartar, bad breath, swollen gums (gum abscess)', without having to indicate which one(s) is responsible. Furthermore, other symptoms which may have been caused by periodontitis are a separate item (and not counted as due to periodontitis) such as, 'missing tooth/ teeth' or 'space between teeth'. This means that the condition-specific score may be under-estimated. Other limitations of the OIDP questionnaire used in these studies was that it was paper-based and as such, some questions (or aspects of) were missed. The research team tried to minimise this, by checking the questionnaire directly following participant completion, however inevitably due to human error, some questions were still overlooked. In all studies, this

missing data was determined to be less than 10% of all questionnaires and the decision was made to exclude those participants. Other options to adjust for this missing data could have been via an intention to treat analysis by means of, 'last observation carried forward' or via multiple imputation methodology. In adjusting for missing data statistically, the magnitude of change is likely to be more conservative.

The follow-up periods presented in this PhD varied, depending on the study, and this may be seen as both a limitation and a strength. The time points to administer the questionnaires were chosen largely arbitrarily, with most clinical trials in the literature administering PROMs at baseline and at one time point following treatment. In chapter 4, a time point of 6-8 weeks following therapy was chosen, as this was generally when a re-evaluation of NST was carried out in the postgraduate clinics at the Eastman Dental Hospital (coinciding with early healing of connective tissues). To contrast, the questionnaires were administered 12 months following therapy in the RCT in chapter 6. One reason is that in general, surgical therapy requires a longer period of healing before re-evaluation (usually 3 months), however, this time point coincided with the final evaluation of diabetic status and clinical outcomes also. The disadvantage of longer time intervals between administering a questionnaire was the susceptibility to recall bias, as participants often had to answer the questionnaire based on the past 3 months. [redacted]

[redacted]

8.3.5 Other

The data had the potential to be explored further (both qualitatively and quantitatively), and due to time constraints, this was not completed. The EQ-5D questionnaire was used (along with the CS-OIDP) to measure quality of life before and after treatment and to note their relationship. A logical next step would be to utilise the values form the EQ-5D to estimate quality-adjusted life year (gains or losses) in economic evaluations of interventions, which alongside the clinical and PROMs, would form a more complete picture when comparing a variety of treatments.

In summary, a number of limitations of this PhD exist, however these have been acknowledged where possible, therefore the results of this thesis have been conservatively presented and should be interpreted with caution. Nevertheless, the findings found herein may be used as a basis for future research on the topic.

8.4 Implications for Future Research, Practice and Policy

The opportunity to evaluate a greater number of treatment options in the treatment of periodontitis in this PhD was not possible due to time and funding restraints. Future research should consider PROMs as a primary outcome measure, which aims to investigate different treatment approaches in a variety of populations (including one or more co-morbidities) longitudinally. The minimally important difference should also be calculated to assist in interpreting the relevance of quality of life results.

Development of a PROM specifically for use in periodontal research would be an ideal next step. The need for a tool which is sufficiently sensitive and responsive to detect change following different modalities of may lead to better clarity on the impact of treatment from the patient's perspective. Additionally, the most appropriate time points to administer PROMs should be investigated.

This thesis has highlighted the need for long-term studies which include PROMs in SPC. This would help to understand the priorities of patients in periodontal maintenance and tailor treatment more effectively to wants and needs. Potentially, this could help with patient education, motivation and ownership of the disease.

The regular use of PROMs in periodontology has a number of implications for practice and policy. Greater knowledge and understanding of how periodontitis and different treatments affect the patient, means that treatment can be more patient-centred, taking into consideration individual preferences and needs, ultimately improving the quality of care. Furthermore, evaluating PROMs in conjunction with clinical outcomes allows clinicians to better educate their patients, increasing health literacy and subsequent shared decision-making. PROMs also allow researchers to include outcomes which are important to the patient, making results more relevant and tangible for the patient.

PROMs also have the important potential to provide the basis for health economic evaluations, essential to assist decision-making and influence resource allocation to those treatments of greatest benefit. This has significant implications for promoting the cost-effectiveness of not just treating established periodontitis, but potentially highlighting the need for prevention of periodontitis altogether through the elimination of gingivitis. Economic modelling based on six European countries has demonstrated that the benefits of investing in prevention strategies (i.e., elimination of gingivitis, as the precursor of periodontitis) and efficiently diagnosing and treating periodontitis has significant

benefit with regard to 'healthy life years' gained and a positive return on investment, compared with just continuing as we are (Economist Intelligence Network, 2021). Furthermore, the recently updated NICE guideline for the management of type 1 and 2 diabetes (National Institute for Health and Care Excellence, 2022b), highlights in their economic evaluation that overall NST is a cost-effective treatment for periodontitis in patients living with diabetes. Other treatments (such as ST) were not evaluated, thus further research in this area is still required, with the potential to influence policy for these patients further.

8.5 Conclusions

OHRQoL improves following treatment of stage III/ IV periodontitis, irrespective of treatment modality and benefits patients with and without a co-morbidity such as diabetes. Self-rated periodontal and general health, and QoL also improves following therapeutic interventions, however this does not appear to be reflected in PROMs evaluating general QoL.

It might be expected that 20-30% of patients attain a meaningful change (above the minimally important difference) in OHRQoL following treatment in both the short and medium term with the MID value estimated to be approximately 5 scale points (4.68 -5.32). Further research needs to be conducted in order to increase the accuracy of the MID estimation in different populations and with different treatments.

The research presented in this thesis contributes to the evidence base supporting the benefits of periodontal therapy on OHRQoL, including patients with co-morbidities such as diabetes. Additionally, priority research areas have been highlighted particularly evaluating OHRQoL in long-term SPC and patients living with other/ multiple co-morbidities.

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APPENDICES

Appendix A. Oral Impacts on Daily Performance Questionnaire and Single-Item Questions.

ORAL IMPACTS ON DAILY PERFORMANCE (OIDP)
SELF-ADMINISTERED QUESTIONNAIRE

This questionnaire is an accepted set of questions designed to assess the effect of gum disease on your mouth. You may find some of these questions unusual. Please make your best try at answering them.

Please answer the following questions and circle the number corresponding to what better represents your experience.

Difficulty eating

1a. Have you had any **difficulty eating** due to the condition of your gums, mouth and teeth (or false teeth) in the past 6 months?

Yes	**1**	→ *ANSWER QUESTIONS 1b TO 1d*
No	**2**	→ *GO TO QUESTION 2a (Difficulty Speaking)*

1b. How often have you had this difficulty eating due to the condition of your mouth and teeth (or false teeth) in the past 6 months?

less often than once a month	**1**
about 1-2 times a month	**2**
about 1-2 times a week	**3**
about 3-4 times a week	**4**
every day or nearly every day	**5**

1c. Using the scale below from 0 to 5, where 0 is no effect and 5 is a very severe effect, can you tell us what **effect** difficulty eating has had **on your daily life** in the past 6 months?

0 1 2 3 4 5

no effect **very severe effect**

1d. And which of the following groups of oral conditions have **caused** this difficulty eating?
PLEASE CIRCLE ALL THAT APPLY

Toothache, sensitive tooth, tooth decay (hole in tooth)	**1**
Loose tooth, bleeding gums, receding gums, tartar, bad breath, swollen gums (gum abscess)	**2**
Bad position of teeth (e.g. crooked or projecting, gap), space between teeth, deformity of the mouth or face	**3**
Broken or fractured tooth	**4**
Missing tooth/teeth	**5**
Colour, shape or size of teeth	**6**
Loose or ill-fitting denture	**7**
Or any other reasons? (please specify)	**8**
None of these	**9**

Difficulty speaking

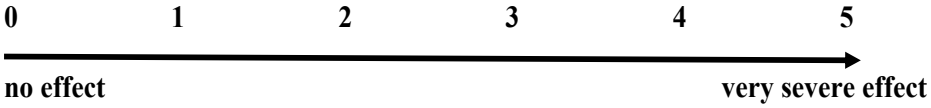
2a. Have you had any **difficulty speaking** due to the condition of your gums, mouth and teeth (or false teeth) in the past 6 months?

Yes	**1**	→ *ANSWER QUESTIONS 2b TO 2d*
No	**2**	→ *GO TO QUESTION 3a (Difficulty Cleaning)*

2b. How often have you had this difficulty speaking due to the condition of your mouth and teeth (or false teeth) in the past 6 months?

less often than once a month	**1**
about 1-2 times a month	**2**
about 1-2 times a week	**3**
about 3-4 times a week	**4**
every day or nearly every day	**5**

2c. Using the scale below from 0 to 5, where 0 is no effect and 5 is a very severe effect, can you tell us what **effect** difficulty speaking has had **on your daily life** in the past 6 months?



2d. And which of the following groups of oral conditions have **caused** this difficulty speaking?
PLEASE CIRCLE ALL THAT APPLY

Toothache, sensitive tooth, tooth decay (hole in tooth)	**1**
Loose tooth, bleeding gums, receding gums, tartar, bad breath, swollen gums (gum abscess)	**2**
Bad position of teeth (e.g. crooked or projecting, gap), space between teeth, deformity of the mouth or face	**3**
Broken or fractured tooth	**4**
Missing tooth/teeth	**5**
Colour, shape or size of teeth	**6**
Loose or ill-fitting denture	**7**
Or any other reasons? (please specify)	**8**
None of these	**9**

Difficulty cleaning your teeth or dentures

3a. Have you had any **difficulty cleaning your teeth or dentures** due to the condition of your gums, mouth and teeth (or false teeth) in the past 6 months?

Yes	**1**	→ *ANSWER QUESTIONS 3b TO 3d*
No	**2**	→ *GO TO QUESTION 4a (Difficulty Going out)*

3b. How often have you had this difficulty cleaning your teeth or dentures due to the condition of your mouth and teeth (or false teeth) in the past 6 months?

less often than once a month	**1**
about 1-2 times a month	**2**
about 1-2 times a week	**3**
about 3-4 times a week	**4**
every day or nearly every day	**5**

3c. Using the scale below from 0 to 5, where 0 is no effect and 5 is a very severe effect, can you tell us what **effect** difficulty cleaning your teeth or dentures has had **on your daily life** in the past 6 months?

0 1 2 3 4 5

no effect **very severe effect**

3d. And which of the following groups of oral conditions have **caused** this difficulty cleaning your teeth or dentures?
PLEASE CIRCLE ALL THAT APPLY

Toothache, sensitive tooth, tooth decay (hole in tooth)	**1**
Loose tooth, bleeding gums, receding gums, tartar, bad breath, swollen gums (gum abscess)	**2**
Bad position of teeth (e.g. crooked or projecting, gap), space between teeth, deformity of the mouth or face	**3**
Broken or fractured tooth	**4**
Missing tooth/teeth	**5**
Colour, shape or size of teeth	**6**
Loose or ill-fitting denture	**7**
Or any other reasons? (please specify)	**8**
None of these	**9**

Difficulty going out

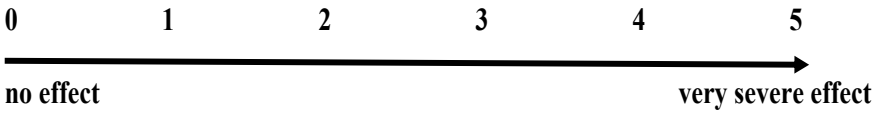
4a. Have you had any **difficulty going out**, for example to the shops or visiting someone, due to the condition of your gums, mouth and teeth (or false teeth) in the past 6 months?

Yes	**1**	→ *ANSWER QUESTIONS 4b TO 4d*
No	**2**	→ *GO TO QUESTION 5a (Difficulty Relaxing)*

4b. How often have you had this difficulty going out, for example to the shops or visiting someone, due to the condition of your mouth and teeth (or false teeth) in the past 6 months?

less often than once a month	**1**
about 1-2 times a month	**2**
about 1-2 times a week	**3**
about 3-4 times a week	**4**
every day or nearly every day	**5**

4c. Using the scale below from 0 to 5, where 0 is no effect and 5 is a very severe effect, can you tell us what **effect** difficulty going out, for example to the shops or visiting someone, has had **on your daily life** in the past 6 months?



4d. And which of the following groups of oral conditions have **caused** this difficulty going out, for example to the shops or visiting someone?
PLEASE CIRCLE ALL THAT APPLY

Toothache, sensitive tooth, tooth decay (hole in tooth)	**1**
Loose tooth, bleeding gums, receding gums, tartar, bad breath, swollen gums (gum abscess)	**2**
Bad position of teeth (e.g. crooked or projecting, gap), space between teeth, deformity of the mouth or face	**3**
Broken or fractured tooth	**4**
Missing tooth/teeth	**5**
Colour, shape or size of teeth	**6**
Loose or ill-fitting denture	**7**
Or any other reasons? (please specify)	**8**
None of these	**9**

Difficulty relaxing

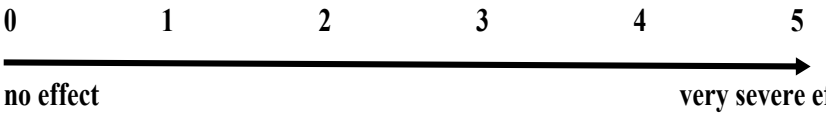
5a. Have you had any **difficulty relaxing** (including sleeping) due to the condition of your gums, mouth and teeth (or false teeth) in the past 6 months?

Yes	**1**	→ *ANSWER QUESTIONS 5b TO 5d*
No	**2**	→ *GO TO QUESTION 6a (Problems with Smiling)*

5b. How often have you had this difficulty relaxing (including sleeping) due to the condition of your gums, mouth and teeth (or false teeth) in the past 6 months?

less often than once a month	**1**
about 1-2 times a month	**2**
about 1-2 times a week	**3**
about 3-4 times a week	**4**
every day or nearly every day	**5**

5c. Using the scale below from 0 to 5, where 0 is no effect and 5 is a very severe effect, can you tell us what **effect** difficulty relaxing (including sleeping) has had **on your daily life** in the past 6 months?



5d. And which of the following groups of oral conditions have **caused** this difficulty relaxing (including sleeping)?
PLEASE CIRCLE ALL THAT APPLY

Toothache, sensitive tooth, tooth decay (hole in tooth)	**1**
Loose tooth, bleeding gums, receding gums, tartar, bad breath, swollen gums (gum abscess)	**2**
Bad position of teeth (e.g. crooked or projecting, gap), space between teeth, deformity of the mouth or face	**3**
Broken or fractured tooth	**4**
Missing tooth/teeth	**5**
Colour, shape or size of teeth	**6**
Loose or ill-fitting denture	**7**
Or any other reasons? (please specify)	**8**
None of these	**9**

Problems with smiling, laughing and showing teeth without embarrassment

6a. Have you had any **problems smiling, laughing and showing teeth without embarrassment** due to the condition of your gums, mouth and teeth (or false teeth) in the past 6 months?

Yes	**1**	→ *ANSWER QUESTIONS 6b TO 6d*
No	**2**	→ *GO TO QUESTION 7a (Difficulty Working)*

6b. How often have you had these problems smiling, laughing and showing teeth without embarrassment due to the condition of your mouth and teeth (or false teeth) in the past 6 months?

less often than once a month	**1**
about 1-2 times a month	**2**
about 1-2 times a week	**3**
about 3-4 times a week	**4**
every day or nearly every day	**5**

6c. Using the scale below from 0 to 5, where 0 is no effect and 5 is a very severe effect, can you tell us what **effect** these problems smiling, laughing and showing teeth without embarrassment have had **on your daily life** in the past 6 months?

0 1 2 3 4 5

→

no effect **very severe effect**

6d. And which of the following groups of oral conditions have **caused** these problems smiling, laughing and showing teeth without embarrassment?
PLEASE CIRCLE ALL THAT APPLY

Toothache, sensitive tooth, tooth decay (hole in tooth)	**1**
Loose tooth, bleeding gums, receding gums, tartar, bad breath, swollen gums (gum abscess)	**2**
Bad position of teeth (e.g. crooked or projecting, gap), space between teeth, deformity of the mouth or face	**3**
Broken or fractured tooth	**4**
Missing tooth/teeth	**5**
Colour, shape or size of teeth	**6**
Loose or ill-fitting denture	**7**
Or any other reasons? (please specify)	**8**
None of these	**9**

Difficulty carrying out your major work or role

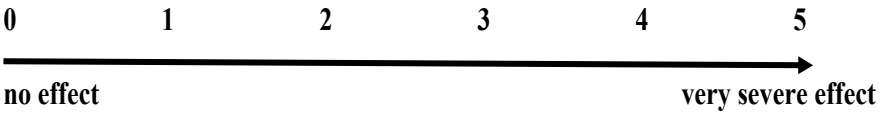
7a. Have you had any **difficulty carrying out your major work or role** due to the condition of your gums, mouth and teeth (or false teeth) in the past 6 months?

Yes	**1**	→ *ANSWER QUESTIONS 7b TO 7d*
No	**2**	→ *GO TO QUESTION 8a (Emotional Problems)*

7b. How often have you had this difficulty carrying out your major work or role due to the condition of your gums, mouth and teeth (or false teeth) in the past 6 months?

less often than once a month	**1**
about 1-2 times a month	**2**
about 1-2 times a week	**3**
about 3-4 times a week	**4**
every day or nearly every day	**5**

7c. Using the scale below from 0 to 5, where 0 is no effect and 5 is a very severe effect, can you tell us what **effect** this difficulty carrying out your major work or role has had **on your daily life** in the past 6 months?



7d. And which of the following groups of oral conditions have **caused** this difficulty carrying out your major work or role?
PLEASE CIRCLE ALL THAT APPLY

Toothache, sensitive tooth, tooth decay (hole in tooth)	**1**
Loose tooth, bleeding gums, receding gums, tartar, bad breath, swollen gums (gum abscess)	**2**
Bad position of teeth (e.g. crooked or projecting, gap), space between teeth, deformity of the mouth or face	**3**
Broken or fractured tooth	**4**
Missing tooth/teeth	**5**
Colour, shape or size of teeth	**6**
Loose or ill-fitting denture	**7**
Or any other reasons? (please specify)	**8**
None of these	**9**

Problems with emotional instability

8a. Have you had any **problems with emotional instability, for example becoming more easily upset than usual,** due to the condition of your gums, mouth and teeth (or false teeth) in the past 6 months?

Yes	**1**	→ *ANSWER QUESTIONS 8b TO 8d*
No	**2**	→ *GO TO QUESTION 9a (Problems with Social Contacts)*

8b. How often have you had these problems with emotional instability, for example becoming more easily upset than usual, due to the condition of your mouth and teeth (or false teeth) in the past 6 months?

less often than once a month	**1**
about 1-2 times a month	**2**
about 1-2 times a week	**3**
about 3-4 times a week	**4**
every day or nearly every day	**5**

8c. Using the scale below from 0 to 5, where 0 is no effect and 5 is a very severe effect, can you tell us what **effect** these problems with emotional instability, for example becoming more easily upset than usual, have had **on your daily life** in the past 6 months?

0 1 2 3 4 5

→

no effect **very severe effect**

8d. And which of the following groups of oral conditions have **caused** these problems with emotional instability, for example becoming more easily upset than usual?
PLEASE CIRCLE ALL THAT APPLY

Toothache, sensitive tooth, tooth decay (hole in tooth)	**1**
Loose tooth, bleeding gums, receding gums, tartar, bad breath, swollen gums (gum abscess)	**2**
Bad position of teeth (e.g. crooked or projecting, gap), space between teeth, Deformity of the mouth or face	**3**
Broken or fractured tooth	**4**
Missing tooth/teeth	**5**
Colour, shape or size of teeth	**6**
Loose or ill-fitting denture	**7**
Or any other reasons? (please specify)	**8**
None of these	**9**

Problems enjoying the contact of other people

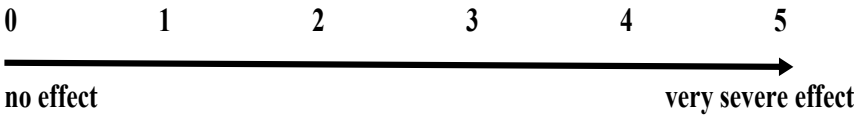
9a. Have you had any **problems enjoying the contact of other people, such as relatives, friends or neighbours,** due to the condition of your gums, mouth and teeth (or false teeth) in the past 6 months?

Yes	**1**	→ *ANSWER QUESTIONS 9b TO 9d*
No	**2**	→ *GO TO QUESTION 10*

9b. How often have you had these problems enjoying the contact of other people, such as relatives, friends or neighbours, due to the condition of your mouth and teeth (or false teeth) in the past 6 months?

less often than once a month	**1**
about 1-2 times a month	**2**
about 1-2 times a week	**3**
about 3-4 times a week	**4**
every day or nearly every day	**5**

9c. Using the scale below from 0 to 5, where 0 is no effect and 5 is a very severe effect, can you tell us what **effect** these problems enjoying the contact of other people, such as relatives, friends or neighbours, have had **on your daily life** in the past 6 months?



9d. And which of the following groups of oral conditions have **caused** these problems enjoying the contact of other people, such as relatives, friends or neighbours?
PLEASE CIRCLE ALL THAT APPLY

Toothache, sensitive tooth, tooth decay (hole in tooth)	**1**
Loose tooth, bleeding gums, receding gums, tartar, bad breath, swollen gums (gum abscess)	**2**
Bad position of teeth (e.g. crooked or projecting, gap), space between teeth, deformity of the mouth or face	**3**
Broken or fractured tooth	**4**
Missing tooth/teeth	**5**
Colour, shape or size of teeth	**6**
Loose or ill-fitting denture	**7**
Or any other reasons? (please specify)	**8**
None of these	**9**

General questions about health and quality of life

10. How is your **health** in general? Would you say it is…

Very good	**1**
Good	**2**
Fair	**3**
Bad	**4**
Or very bad?	**5**

11. And would you say your **dental health** in general is…

Very good	**1**
Good	**2**
Fair	**3**
Bad	**4**
Or very bad?	**5**

12. How about your periodontal health (i.e. the health of your gums)? Would you say it is in general…

Very good	**1**
Good	**2**
Fair	**3**
Bad	**4**
Or very bad?	**5**

13. Since completion of periodontal treatment at the clinic has your periodontal health (*Do not answer this question if this is your first time completing this questionnaire*) …

Worsened a lot	**1**
Worsened a little	**2**
Stayed the same	**3**
Improved a little	**4**
Or improved a lot?	**5**

14. Throughout this questionnaire, we have asked you about a number of different problems that you may have experienced because of the condition of your gums, mouth and teeth (or false teeth). To what extent have you been **bothered by these problems**?

Not at all	**1**
A little	**2**
Somewhat	**3**
A fair amount	**4**
Or a great deal?	**5**

15. Throughout this questionnaire, we have asked you about a number of different problems that you may have experienced because of the condition of your gums, mouth and teeth (or false teeth). To what extent have these problems **affected your life overall?**

Not at all	**1**
A little	**2**

Somewhat	**3**
A fair amount	**4**
Or a great deal?	**5**

16. Throughout this questionnaire, we have asked you about a number of different problems that you may have experienced because of the condition of your gums, mouth and teeth (or false teeth). To what extent have these problems **affected your quality of life?**

Not at all	**1**
A little	**2**
Somewhat	**3**
A fair amount	**4**
Or a great deal?	**5**

17. How would you rate the quality of your life?

Excellent	**1**
Very good	**2**
Good	**3**
Fair	**4**
Poor	**5**
Very poor	**6**

18. Finally, we would like to ask two questions pertaining to attained education.

A) At what age did you finish your continuous full-time education at school or college?

i. Not yet finished
ii. Never went to school
iii. 14 or under
iv. 15
v. 16
vi. 17
vii. 18
viii. 19 or over

B) What is the highest level of education you have completed?

i. Pre-primary education (early childhood education) – ISCED Level 0

ii. Primary education (usually the first six years of formal schooling) – ISCED Level 1

iii. Lower secondary education (usually coincides with the end of full-time compulsory schooling after around nine years of schooling) – ISCED Level 2

iv. Upper secondary education (where university entrance certificates and vocational qualifications which require completion of level 2 are awarded) – ISCED Level 3

v. Post-secondary non-tertiary education (programmes that straddle the boundary between level 3 and 5, e.g. university entrance certificates for adults or non-tertiary vocational education after general upper secondary) – ISCED Level 4

vi. First stage of tertiary education (all university and vocational college education exclusive of PhD/doctorate and equivalent) – ISCED Level 5

vii. Second stage of tertiary education (leading to an advanced research qualification, i.e. PhD/doctorate and equivalent) – ISCED Level 6

END OF PART I
PLEASE PROCEED TO PART II

Appendix B. EQ-5D-3L Questionnaire

Patient Initials: _____	Protocol Perio-07-30	Subject # : _____

Health Questionnaire

English version for the UK
(validated for Ireland)

Patient Initials: _____	Protocol Perio-07-30	Subject # : _____

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

I have some problems washing or dressing myself ❑

I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*

I have no problems with performing my usual activities ❑

I have some problems with performing my usual activities ❑

I am unable to perform my usual activities ❑

Pain/Discomfort

I have no pain or discomfort ❑

I have moderate pain or discomfort ❑

I have extreme pain or discomfort ❑

Anxiety/Depression

I am not anxious or depressed ❑

I am moderately anxious or depressed ❑

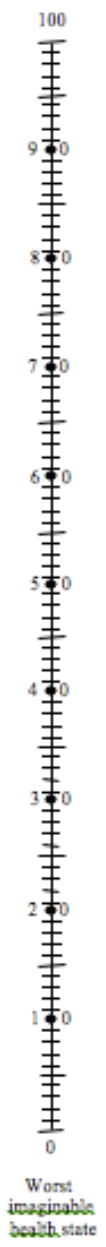
I am extremely anxious or depressed ❑

Patient Initials: _____	Protocol Perio-07-30	Subject #.: _____

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.

Your own health state today



YOU HAVE FINISHED.
PLEASE MAKE SURE THAT YOU HAVE ANSWERED ALL THE RELEVANT QUESTIONS.
THANK YOU VERY MUCH FOR YOUR TIME AND EFFORT.

Questionnaire completion has been checked by:_____ on: ___ / ___ / ___

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Appendix C. CONSORT Checklist Extension for Non-Pharmacologic Trials

Section/Topic Item	Checklist item no.	CONSORT item	Extension for NPT trials
Title and abstract			
	1a	Identification as a randomized trial in the title pg. 100	
	1b	Structured summary of trial design, methods, results, and conclusions (for specific guidance see CONSORT for abstracts) N/A	*Refer to CONSORT extension for abstracts for NPT trials*
Introduction			
Background and objectives	2a	Scientific background and explanation of rationale pg. 31-35, 100	
	2b	Specific objectives or hypotheses pg. 100	
Methods			
Trial design	3a	Description of trial design (such as parallel, factorial) including allocation ratio pg. 103	When applicable, how care providers were allocated to each trial group pg. 104
	3b	Important changes to methods after trial commencement (such as eligibility criteria), with reasons N/A	

Section/Topic Item	Checklist item no.	CONSORT item	Extension for NPT trials
Participants	4a	Eligibility criteria for participants pg.102	When applicable, eligibility criteria for centers and for *care providers* N/A
	4b	Settings and locations where the data were collected pg. 104	
Interventions†	5	The interventions for each group with sufficient details to allow replication, including how and when they were actually administered pg. 107-110	Precise details of both the experimental treatment and comparator Pg. 107-110
	5a		Description of the different components of the interventions and, when applicable, description of the procedure for tailoring the interventions to individual participants. Pg. 107-110
	5b		Details *of whether and* how the interventions were standardized. Pg. 104
	5c.		Details *of whether and* how adherence of care providers to the protocol was assessed or enhanced pg. 109

Section/Topic Item	Checklist item no.	CONSORT item	Extension for NPT trials
	5d		*Details of whether and how adherence of participants to interventions was assessed or enhanced*
Outcomes	6a	Completely defined pre-specified primary and secondary outcome measures, including how and when they were assessed pg. 103	
	6b	Any changes to trial outcomes after the trial commenced, with reasons	
Sample size	7a	How sample size was determined pg. 103	When applicable, details of whether and how the clustering by care providers or centers was addressed
	7b	When applicable, explanation of any interim analyses and stopping guidelines	
Randomization:			
- Sequence generation	8a	Method used to generate the random allocation sequence pg. 104	

Section/Topic Item	Checklist item no.	CONSORT item	Extension for NPT trials
	8b	Type of randomization; details of any restriction (such as blocking and block size) pg. 104	
- Allocation concealment mechanism	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 pg. 105	
- Implementation	10	Who generated the random allocation sequence, who enrolled participants, and who assigned participants to interventions pg. 105	
Blinding	11a	If done, who was blinded after assignment to interventions (for example, participants, care providers, those assessing outcomes) and how Pg. 110	~~Whether or not those administering co-interventions were blinded to group assignment~~ If done, who was blinded after assignment to interventions (e.g., participants, care providers, *those administering co-interventions,* those assessing outcomes) and how

Section/Topic Item	Checklist item no.	CONSORT item	Extension for NPT trials
	11b	If relevant, description of the similarity of interventions	~~If blinded, method of blinding and description of the similarity of interventions~~
	11c		*If blinding was not possible, description of any attempts to limit bias*
Statistical methods	12a	Statistical methods used to compare groups for primary and secondary outcomes pg. 114	When applicable, details of whether and how the clustering by care providers or centers was addressed
	12b	Methods for additional analyses, such as subgroup analyses and adjusted analyses	
Results			
Participant flow (a diagram is strongly recommended)	13a	For each group, the numbers of participants who were randomly assigned, received intended treatment, and were analyzed for the primary outcome pg. 116	The number of care providers or centers performing the intervention in each group and the number of patients treated by each care provider or in each center
	13b	For each group, losses and exclusions after randomization, together with reasons pg. 115	

Section/Topic Item	Checklist item no.	CONSORT item	Extension for NPT trials
	13c		*For each group, the delay between randomization and the initiation of the intervention*
	new		Details of the experimental treatment and comparator as they were implemented
Recruitment	14a	Dates defining the periods of recruitment and follow-up	
	14b	Why the trial ended or was stopped	
Baseline data	15	A table showing baseline demographic and clinical characteristics for each group pg. 118-119	When applicable, a description of care providers (case volume, qualification, expertise, etc.) and centers (volume) in each group.
Numbers analyzed	16	For each group, number of participants (denominator) included in each analysis and whether the analysis was by original assigned groups pg.118-121	

Section/Topic Item	Checklist item no.	CONSORT item	Extension for NPT trials
Outcomes and estimation	17a	For each primary and secondary outcome, results for each group, and the estimated effect size and its precision (such as 95% confidence interval)	
	17b	For binary outcomes, presentation of both absolute and relative effect sizes is recommended	
Ancillary analyses	18	Results of any other analyses performed, including subgroup analyses and adjusted analyses, distinguishing pre-specified from exploratory	
Harms	19	All important harms or unintended effects in each group (for specific guidance see CONSORT for harms)	
Discussion			
Limitations	20	Trial limitations, addressing sources of potential bias, imprecision, and, if relevant, multiplicity of analyses pg.158	In addition, take into account the choice of the comparator, lack of or partial blinding, and unequal expertise of care providers or centers in each group pg. 159

Section/Topic Item	Checklist item no.	CONSORT item	Extension for NPT trials
Generalizability	21	Generalizability (external validity, applicability) of the trial findings pg. 159	Generalizability (external validity) of the trial findings according to the intervention, comparators, patients, and care providers and centers involved in the trial
Interpretation	22	Interpretation consistent with results, balancing benefits and harms, and considering other relevant evidence	
Other information			
Registration	23	Registration number and name of trial registry pg. 101	
Protocol	24	Where the full trial protocol can be accessed, if available	
Funding	25	Sources of funding and other support (such as supply of drugs), role of funders	

[redacted]

Appendix E. Oral Impacts on Daily Performance Questionnaire

ORAL IMPACTS ON DAILY PERFORMANCE (OIDP) Date_____
SELF-ADMINISTERED QUESTIONNAIRE – PAST 3 MONTHS

The following questions are about your oral health and how it may affect your quality of life. We would like to know whether you had any difficulties or problems with some everyday activities and behaviors caused by your mouth, teeth or false teeth (dentures).

Please answer the following questions and circle the number corresponding to what better represents your experience.

Difficulty eating

1a. Have you had any **difficulty eating** due to the condition of your mouth and teeth (or false teeth) in the past 3 months?

Yes	**1**	→ *ANSWER QUESTIONS 1b TO 1d*
No	**2**	→ *GO TO QUESTION 2a (Difficulty Speaking)*

1b. How often have you had this difficulty eating due to the condition of your mouth and teeth (or false teeth) in the past 3 months?

less often than once a month	**1**
about 1-2 times a month	**2**
about 1-2 times a week	**3**
about 3-4 times a week	**4**
every day or nearly every day	**5**

1c. Using the scale below from 0 to 5, where 0 is no effect and 5 is a very severe effect, can you tell us what **effect** this difficulty eating has had **on your daily life** in the past 3 months?

0 1 2 3 4 5

no effect → **very severe effect**

1d. And which of the following groups of oral conditions have **caused** this difficulty eating?
PLEASE CIRCLE ALL THAT APPLY

Toothache, sensitive tooth, tooth decay (hole in tooth)	**1**
Loose tooth, bleeding gums, receding gums, tartar, bad breath, swollen gums (gum abscess)	**2**
Bad position of teeth (e.g. crooked or projecting, gap), space between teeth, deformity of the mouth or face	**3**
Broken or fractured tooth	**4**
Missing tooth/teeth	**5**
Colour, shape or size of teeth	**6**
loose or ill-fitting denture	**7**
Or any other reasons? (please specify)	**8**
None of these	**9**

Difficulty speaking

2a. Have you had any **difficulty speaking** due to the condition of your mouth and teeth (or false teeth) in the past 3 months?

Yes	**1**	→ *ANSWER QUESTIONS 2b TO 2d*
No	**2**	→ *GO TO QUESTION 3a (Difficulty Cleaning)*

2b. How often have you had this difficulty speaking due to the condition of your mouth and teeth (or false teeth) in the past 3 months?

less often than once a month	**1**
about 1-2 times a month	**2**
about 1-2 times a week	**3**
about 3-4 times a week	**4**
every day or nearly every day	**5**

2c. Using the scale below from 0 to 5, where 0 is no effect and 5 is a very severe effect, can you tell us what **effect** this difficulty speaking has had **on your daily life** in the past 3 months?

0 1 2 3 4 5

no effect → **very severe effect**

2d. And which of the following groups of oral conditions have **caused** this difficulty speaking?
PLEASE CIRCLE ALL THAT APPLY

Toothache, sensitive tooth, tooth decay (hole in tooth)	**1**
Loose tooth, bleeding gums, receding gums, tartar, bad breath, swollen gums (gum abscess)	**2**
Bad position of teeth (e.g. crooked or projecting, gap), space between teeth, deformity of the mouth or face	**3**
Broken or fractured tooth	**4**
Missing tooth/teeth	**5**
Colour, shape or size of teeth	**6**
loose or ill-fitting denture	**7**
Or any other reasons? (please specify)	**8**
None of these	**9**

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Difficulty cleaning your teeth or dentures

3a. Have you had any **difficulty cleaning your teeth or dentures** due to the condition of your mouth and teeth (or false teeth) in the past 3 months?

Yes	**1**	→ *ANSWER QUESTIONS 3b TO 3d*
No	**2**	→ *GO TO QUESTION 4a (Difficulty Going out)*

3b. How often have you had this difficulty cleaning your teeth or dentures due to the condition of your mouth and teeth (or false teeth) in the past 3 months?

less often than once a month	**1**
about 1-2 times a month	**2**
about 1-2 times a week	**3**
about 3-4 times a week	**4**
every day or nearly every day	**5**

3c. Using the scale below from 0 to 5, where 0 is no effect and 5 is a very severe effect, can you tell us what **effect** this difficulty cleaning your teeth or dentures has had **on your daily life** in the past 3 months?

0 1 2 3 4 5

no effect → **very severe effect**

3d. And which of the following groups of oral conditions have **caused** this difficulty cleaning your teeth or dentures?
PLEASE CIRCLE ALL THAT APPLY

Toothache, sensitive tooth, tooth decay (hole in tooth)	**1**
Loose tooth, bleeding gums, receding gums, tartar, bad breath, swollen gums (gum abscess)	**2**
Bad position of teeth (e.g. crooked or projecting, gap), space between teeth, deformity of the mouth or face	**3**
Broken or fractured tooth	**4**
Missing tooth/teeth	**5**
Colour, shape or size of teeth	**6**
loose or ill-fitting denture	**7**
Or any other reasons? (please specify)	**8**
None of these	**9**

Difficulty going out

4a. Have you had any **difficulty going out**, for example to the shops or visiting someone, due to the condition of your mouth and teeth (or false teeth) in the past 3 months?

Yes	**1**	→ *ANSWER QUESTIONS 4b TO 4d*
No	**2**	→ *GO TO QUESTION 5a (Difficulty Relaxing)*

4b. How often have you had this difficulty going out, for example to the shops or visiting someone, due to the condition of your mouth and teeth (or false teeth) in the past 3 months?

less often than once a month	**1**
about 1-2 times a month	**2**
about 1-2 times a week	**3**
about 3-4 times a week	**4**
every day or nearly every day	**5**

4c. Using the scale below from 0 to 5, where 0 is no effect and 5 is a very severe effect, can you tell us what **effect** this difficulty going out, has had **on your daily life** in the past 3 months?

0 1 2 3 4 5

no effect → **very severe effect**

4d. And which of the following groups of oral conditions have **caused** this difficulty going out?
PLEASE CIRCLE ALL THAT APPLY

Toothache, sensitive tooth, tooth decay (hole in tooth)	**1**
Loose tooth, bleeding gums, receding gums, tartar, bad breath, swollen gums (gum abscess)	**2**
Bad position of teeth (e.g. crooked or projecting, gap), space between teeth, deformity of the mouth or face	**3**
Broken or fractured tooth	**4**
Missing tooth/teeth	**5**
Colour, shape or size of teeth	**6**
loose or ill-fitting denture	**7**
Or any other reasons? (please specify)	**8**
None of these	**9**

Difficulty relaxing

5a. Have you had any **difficulty relaxing** (including sleeping) due to the condition of your mouth and teeth (or false teeth) in the past 3 months?

Yes	**1**	→ *ANSWER QUESTIONS 5b TO 5d*
No	**2**	→ *GO TO QUESTION 6a (Problems with Smiling)*

5b. How often have you had this difficulty relaxing (including sleeping) due to the condition of your mouth and teeth (or false teeth) in the past 3 months?

less often than once a month	**1**
about 1-2 times a month	**2**
about 1-2 times a week	**3**
about 3-4 times a week	**4**
every day or nearly every day	**5**

5c. Using the scale below from 0 to 5, where 0 is no effect and 5 is a very severe effect, can you tell us what **effect** this difficulty relaxing (including sleeping) has had **on your daily life** in the past 3 months?

0 1 2 3 4 5

no effect **very severe effect**

5d. And which of the following groups of oral conditions have **caused** this difficulty relaxing (including sleeping)?
PLEASE CIRCLE ALL THAT APPLY

Toothache, sensitive tooth, tooth decay (hole in tooth)	**1**
Loose tooth, bleeding gums, receding gums, tartar, bad breath, swollen gums (gum abscess)	**2**
Bad position of teeth (e.g. crooked or projecting, gap), space between teeth, deformity of the mouth or face	**3**
Broken or fractured tooth	**4**
Missing tooth/teeth	**5**
Colour, shape or size of teeth	**6**
loose or ill-fitting denture	**7**
Or any other reasons? (please specify)	**8**
None of these	**9**

Problems with smiling, laughing and showing teeth without embarrassment

6a. Have you had any **problems smiling, laughing and showing teeth without embarrassment** due to the condition of your mouth and teeth (or false teeth) in the past 3 months?

Yes	**1**	→ *ANSWER QUESTIONS 6b TO 6d*
No	**2**	→ *GO TO QUESTION 7a (Difficulty Working)*

6b. How often have you had these problems smiling, laughing and showing teeth without embarrassment due to the condition of your mouth and teeth (or false teeth) in the past 3 months?

less often than once a month	**1**
about 1-2 times a month	**2**
about 1-2 times a week	**3**
about 3-4 times a week	**4**
every day or nearly every day	**5**

6c. Using the scale below from 0 to 5, where 0 is no effect and 5 is a very severe effect, can you tell us what **effect** these problems smiling, laughing and showing teeth without embarrassment have had **on your daily life** in the past 3 months?

0 1 2 3 4 5

no effect → **very severe effect**

6d. And which of the following groups of oral conditions have **caused** these problems smiling, laughing and showing teeth without embarrassment?
PLEASE CIRCLE ALL THAT APPLY

Toothache, sensitive tooth, tooth decay (hole in tooth)	**1**
Loose tooth, bleeding gums, receding gums, tartar, bad breath, swollen gums (gum abscess)	**2**
Bad position of teeth (e.g. crooked or projecting, gap), space between teeth, deformity of the mouth or face	**3**
Broken or fractured tooth	**4**
Missing tooth/teeth	**5**
Colour, shape or size of teeth	**6**
loose or ill-fitting denture	**7**
Or any other reasons? (please specify)	**8**
None of these	**9**

Difficulty carrying out your major work or role

7a. Have you had any **difficulty carrying out your major work or role** due to the condition of your mouth and teeth (or false teeth) in the past 3 months?

Yes	**1**	→ *ANSWER QUESTIONS 7b TO 7d*
No	**2**	→ *GO TO QUESTION 8a (Emotional Problems)*

7b. How often have you had this difficulty carrying out your major work or role due to the condition of your mouth and teeth (or false teeth) in the past 3 months?

less often than once a month	**1**
about 1-2 times a month	**2**
about 1-2 times a week	**3**
about 3-4 times a week	**4**
every day or nearly every day	**5**

7c. Using the scale below from 0 to 5, where 0 is no effect and 5 is a very severe effect, can you tell us what **effect** this difficulty carrying out your major work or role has had **on your daily life** in the past 3 months?

0 1 2 3 4 5

no effect → **very severe effect**

7d. And which of the following groups of oral conditions have **caused** this difficulty carrying out your major work or role?
PLEASE CIRCLE ALL THAT APPLY

Toothache, sensitive tooth, tooth decay (hole in tooth)	**1**
Loose tooth, bleeding gums, receding gums, tartar, bad breath, swollen gums (gum abscess)	**2**
Bad position of teeth (e.g. crooked or projecting, gap), space between teeth, deformity of the mouth or face	**3**
Broken or fractured tooth	**4**
Missing tooth/teeth	**5**
Colour, shape or size of teeth	**6**
loose or ill-fitting denture	**7**
Or any other reasons? (please specify)	**8**
None of these	**9**

Emotional problems

8a. Have you had any **emotional problems, for example becoming more easily upset than usual,** due to the condition of your mouth and teeth (or false teeth) in the past 3 months?

Yes	**1**	→ *ANSWER QUESTIONS 8b TO 8d*
No	**2**	→ *GO TO QUESTION 9a (Problems with Social Contacts)*

8b. How often have you had these emotional problems, for example becoming more easily upset than usual, due to the condition of your mouth and teeth (or false teeth) in the past 3 months?

less often than once a month	**1**
about 1-2 times a month	**2**
about 1-2 times a week	**3**
about 3-4 times a week	**4**
every day or nearly every day	**5**

8c. Using the scale below from 0 to 5, where 0 is no effect and 5 is a very severe effect, can you tell us what **effect** these emotional problems, for example becoming more easily upset than usual, have had **on your daily life** in the past 3 months?

0 1 2 3 4 5

no effect → **very severe effect**

8d. And which of the following groups of oral conditions have **caused** these emotional problems, for example becoming more easily upset than usual?
PLEASE CIRCLE ALL THAT APPLY

Toothache, sensitive tooth, tooth decay (hole in tooth)	**1**
Loose tooth, bleeding gums, receding gums, tartar, bad breath, swollen gums (gum abscess)	**2**
Bad position of teeth (e.g. crooked or projecting, gap), space between teeth, deformity of the mouth or face	**3**
Broken or fractured tooth	**4**
Missing tooth/teeth	**5**
Colour, shape or size of teeth	**6**
loose or ill-fitting denture	**7**
Or any other reasons? (please specify)	**8**
None of these	**9**

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Problems enjoying the contact of other people

9a. Have you had any **problems enjoying the contact of other people, such as relatives, friends or neighbours,** due to the condition of your mouth and teeth (or false teeth) in the past 3 months?

Yes	**1** →	*ANSWER QUESTIONS 9b TO 9d*
No	**2** →	*GO TO QUESTION 10*

9b. How often have you had these problems enjoying the contact of other people, such as relatives, friends or neighbours, due to the condition of your mouth and teeth (or false teeth) in the past 3 months?

less often than once a month	**1**
about 1-2 times a month	**2**
about 1-2 times a week	**3**
about 3-4 times a week	**4**
every day or nearly every day	**5**

9c. Using the scale below from 0 to 5, where 0 is no effect and 5 is a very severe effect, can you tell us what **effect** these problems enjoying the contact of other people, have had **on your daily life** in the past 3 months?

0 1 2 3 4 5

no effect → **very severe effect**

9d. And which of the following groups of oral conditions have **caused** these problems enjoying the contact of other people?
PLEASE CIRCLE ALL THAT APPLY

Toothache, sensitive tooth, tooth decay (hole in tooth)	**1**
Loose tooth, bleeding gums, receding gums, tartar, bad breath, swollen gums (gum abscess)	**2**
Bad position of teeth (e.g. crooked or projecting, gap), space between teeth, deformity of the mouth or face	**3**
Broken or fractured tooth	**4**
Missing tooth/teeth	**5**
Colour, shape or size of teeth	**6**
loose or ill-fitting denture	**7**
Or any other reasons? (please specify)	**8**
None of these	**9**

General questions about health and quality of life

10. How is your **health** in general? Would you say it is…

Very good	**1**
Good	**2**
Fair	**3**
Bad	**4**
Or very bad?	**5**

11. And would you say your **dental health** in general is…

Very good	**1**
Good	**2**
Fair	**3**
Bad	**4**
Or very bad?	**5**

12. How about your periodontal health (i.e. the health of your gums)? Would you say it is in general…

Very good	**1**
Good	**2**
Fair	**3**
Bad	**4**
Or very bad?	**5**

****If this is your baseline (1st study appointment), please go straight to Question 14. However, if this is NOT a baseline appointment, please continue to Question 13.**

13. Since completion of periodontal treatment/ your last visit at the clinic, that is in the past 3 months, has your periodontal health …

Worsened a lot	**1**
Worsened a little	**2**
Stayed the same	**3**
Improved a little	**4**
Or improved a lot?	**5**

14. Throughout this questionnaire, we have asked you about a number of different problems that you may have experienced because of the condition of your mouth and teeth (or false teeth). To what extent have these problems **affected your quality of life overall** in the past 3 months?

Not at all	**1**
A little	**2**
Somewhat	**3**
A fair amount	**4**
Or a great deal?	**5**

YOU HAVE FINISHED.
PLEASE MAKE SURE THAT YOU HAVE ANSWERED ALL THE RELEVANT QUESTIONS.
THANK YOU VERY MUCH FOR YOUR TIME AND EFFORT

Appendix F. EQ-5D-5L Questionnaire

Patient Initials:_____ Subject Number:_____

Visit No:_____

Health Questionnaire

English version for the UK

Patient Initials:_____ Subject Number:_____

Visit No:_____

Under each heading, please tick the ONE box that best describes your health TODAY

MOBILITY

I have no problems in walking about ❑
I have slight problems in walking about ❑
I have moderate problems in walking about ❑
I have severe problems in walking about ❑
I am unable to walk about ❑

SELF-CARE

I have no problems washing or dressing myself ❑
I have slight problems washing or dressing myself ❑
I have moderate problems washing or dressing myself ❑
I have severe problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

USUAL ACTIVITIES *(e.g. work, study, housework, family or leisure activities)*

I have no problems doing my usual activities ❑
I have slight problems doing my usual activities ❑
I have moderate problems doing my usual activities ❑
I have severe problems doing my usual activities ❑
I am unable to do my usual activities ❑

PAIN / DISCOMFORT

I have no pain or discomfort ❑
I have slight pain or discomfort ❑
I have moderate pain or discomfort ❑
I have severe pain or discomfort ❑
I have extreme pain or discomfort ❑

ANXIETY / DEPRESSION

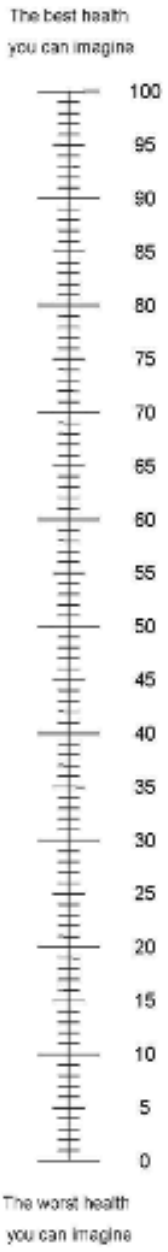
I am not anxious or depressed ❑
I am slightly anxious or depressed ❑
I am moderately anxious or depressed ❑
I am severely anxious or depressed ❑
I am extremely anxious or depressed ❑

Patient Initials:_____ Subject Number:_____

Visit No:_____

- We would like to know how good or bad your health is TODAY.
- This scale is numbered from 0 to 100.
- 100 means the best health you can imagine.
  0 means the worst health you can imagine.
- Mark an X on the scale to indicate how your health is TODAY.
- Now, please write the number you marked on the scale in the box below.

YOUR HEALTH TODAY = ☐



Appendix G. Search Strategy

Ovid MEDLINE(R) and Epub Ahead of Print, In-Process & Other Non-Indexed Citations and Daily from 1946 to 17 July 2021

1	periodontitis/ or aggressive periodontitis/ or chronic periodontitis/ or periodontal abscess/ or periodontal pocket/
2	Periodontal Attachment Loss/
3	Alveolar Bone Loss/
4	periodontit*.tw.
5	periodont* attachment loss.tw
6	(periodontal adj2 pocket*).tw.
7	(bleeding adj3 (probing or probe*)).tw.
8	(alveolar adj2 (loss* or atroph*)).tw.
9	((periodont* or alveolar) adj resorption*).tw.
10	or/1-9
11	supportive periodontal therap*.tw.
12	supportive periodontal care.tw.
13	SPT.tw.
14	((periodont* or dentition or dental or tooth or teeth) adj4 (maintenance or maintain* or posttreat* or post-treat* or prevent*)).tw.
15	(recall maintenance or maintenance therap*).tw
16	preventive maintenance.tw.
17	((post surg* or postsurgic*) adj recall).tw.
18	Secondary prevention/
19	Preventive dentistry/
20	exp Dental prophylaxis/
21	dental prophylaxis.tw.
22	oral prophylaxis.tw.
23	(root adj (plane* or planing)).tw.
24	((Dental or oral or teeth or tooth or supragingival or supra-gingival or subgingival or sub-gingival) adj6 (scaling or scaler* or curettage or curette*)).tw.
25	((periodontal or supra-gingival or supragingival or sub-gingival or subgingival) adj debridement*).tw.

26	Subgingival curettage/
27	exp Diagnosis, Oral/
28	((intraoral or intra-oral or extraoral or extra-oral) adj4 (check-up* or checkup* or inspect* or exam* or attend* or recall* or visit* or diagnos?s)).tw.
29	((dental or oral or teeth or tooth or proximal surface*) adj3 (radiograph* or ex-ray or xray or ex-rays or x-rays)).tw.
30	Radiography, Dental/
31	exp Oral hygiene/
32	oral hygiene.mp.
33	(mouth adj3 hygiene).tw.
34	(mouth adj3 care).tw.
35	(dental adj3 care).tw.
36	(care adj3 teeth).tw
37	(oral adj3 care).tw.
38	plaque control*.tw.
39	(professional adj2 plaque* removal).tw.
40	PMPR.tw.
41	Health Education, Dental/
42	((health adj5 promot*) and (dental or teeth or mouth or periodont* or gingiv* or oral)).tw.
43	(health awar* and (dental or teeth or mouth or periodont* or gingiv* or oral)).tw.
44	((Dental or teeth or mouth or periodont* or gingival or oral) and (instruct* or advis* or advic* or educat* or teach* or train*)).tw.
45	Dental care/
46	Comprehensive Dental care/
47	exp animals/ not humans.sh.
48	or/11-46
49	10 and 48
50	49 not 47
51	limit 50 to english language

Ovid Embase Classic and Embase, from 1947 to 17 July 2021.

1	periodontitis/ or aggressive periodontitis/ or chronic periodontitis/ or periodontal abscess/ or periodontal pocket/
2	alveolar bone loss/
3	periodontit*.tw.
4	periodont* attachment loss.tw.
5	(periodontal adj2 pocket*).tw.
6	(bleeding adj3 (probe* or probing)).tw.
7	(alveolar adj2 (loss* or atroph*)).tw.
8	((periodont* or alveolar) adj resorption*).tw.
9	or/1-8
10	supportive periodontal therap*.tw.
11	supportive periodontal care.tw.
12	SPT.tw.
13	((periodont* or dentition or dental or tooth or teeth) adj4 (maintenance or maintain* or posttreat* or post-treat* or prevent*)).tw
14	recall maintenance.tw.
15	(preventive maintenance or maintenance therap*).tw.
16	((post surg* or postsurgic*) adj recall).tw.
17	secondary prevention/
18	preventive dentistry/
19	exp dental prophylaxis/
20	dental prophylaxis.tw.
21	oral prophylaxis.tw.
22	((Dental or oral or teeth or tooth or supragingival or supra-gingival or subgingival or sub-gingival) adj6 (scaling or scaler* or curettage or curette*)).tw.
23	((periodontal or supra-gingival or supragingival or sub-gingival or subgingival) adj debridement*).tw.
24	(root adj (plane* or planing)).tw.
25	dental curettage/ or periodontal procedure/
26	dental health education/

27	((intraoral or intra-oral or extraoral or extra-oral) adj4 (check-up* or checkup* or inspect* or exam* or attend* or recall* or visit* or diagnos?s)).tw.
28	tooth radiography/
29	((dental or oral or teeth or tooth or proximal surface*) adj3 (radiograph* or ex-ray or xray or ex-rays or x-rays)).tw
30	mouth hygiene/
31	oral hygiene.tw.
32	(mouth adj3 hygiene).tw
33	(mouth adj3 care).tw.
34	(dental adj3 care).tw.
35	(care adj3 teeth).tw
36	(oral adj3 care).tw.
37	plaque control*.tw.
38	(professional adj2 plaque* removal).tw.
39	PMPR.tw.
40	((health adj5 promot*) and (dental or teeth or mouth or periodont* or gingiv* or oral)).tw.
41	(health awar* and (dental or teeth or mouth or periodont* or gingiv* or oral)).tw.
42	((Dental or teeth or mouth or periodont* or gingival or oral) and (instruct* or advis* or advic* or educat* or teach* or train*)).tw.
43	dental prevention/
44	or/10-43
45	9 and 44
46	(exp animal/ or animal.hw. or nonhuman/) not (exp human/ or human cell/ or (human or humans).ti.)
47	45 not 46
48	limit 47 to english language

LILACS VHL Regional Portal (date run 17 July 2021)

tw:((tw:(periodontit* OR "bleeding on probing" OR "bleeding upon probing" OR "alveolar bone loss")) AND (tw:("supportive periodontal therapy" OR "supportive periodontal care" OR "dental prophylaxis" OR "oral prophylaxis" OR "root planing" OR "oral hygiene" OR "mouth care" OR "mouth hygiene" OR "dental care" OR "dental hygiene" OR "oral care" OR "plaque removal" OR "plaque control" OR debridement* OR scaling OR scaler* OR curettage OR radiograph* OR "ex-ray" OR xray OR "ex-rays" OR "x-rays" OR "health promotion" OR check-up* OR checkup* OR "check up" OR "check ups" OR examination* OR recall* OR visit* OR diagnos* OR maintenance OR maintain* OR posttreat* OR post-treat* OR prevent*)) NOT (tw:((mh:animals OR mh:rabbits OR mh:rats OR mh:primates OR mh:dogs OR mh:cats OR mh:swine OR pt:"in vitro")))) AND (db:("LILACS") AND la:("en"))

Cochrane Central Register of Controlled Trials (CENTRAL) (date run 17 July 2021)

#1	MeSH descriptor: [Periodontitis] this term only
#2	MeSH descriptor: [Aggressive Periodontitis] this term only
#3	MeSH descriptor: [Chronic Periodontitis] this term only
#4	MeSH descriptor: [Periodontal Abscess] this term only
#5	MeSH descriptor: [Periodontal Pocket] this term only
#6	MeSH descriptor: [Periodontal Attachment Loss] this term only
#7	MeSH descriptor: [Alveolar Bone Loss] this term only
#8	(periodontit*):ti,ab,kw
#9	(periodont* NEAR/1 "attachment loss"):ti,ab,kw
#10	(periodontal NEAR/1 pocket*):ti,ab,kw
#11	(("bleeding on probing" OR "bleeding upon probing")):ti,ab,kw
#12	(alveolar NEAR/1 (loss* or atroph*)):ti,ab,kw
#13	((periodont* or alveolar) NEAR/2 resorption*):ti,ab,kw
#14	(Tsakos et al. -#13)
#15	(supportive periodontal therap*):ti,ab,kw
#16	(supportive periodontal care):ti,ab,kw
#17	(SPT):ti,ab,kw
#18	((periodont* OR dentition OR dental OR tooth OR teeth) NEAR/3 (maintain* OR maintenance OR posttreat* OR post-treat* OR "post treat*" OR prevent*)):ti,ab,kw
#19	("recall maintenance"):ti,ab,kw
#20	("preventive maintenance"):ti,ab,kw
#21	((post-surg* OR postsurgic* OR "post surg*") NEXT recall):ti,ab,kw
#22	MeSH descriptor: [Secondary Prevention] this term only
#23	MeSH descriptor: [Preventive Dentistry] this term only
#24	MeSH descriptor: [Dental Prophylaxis] explode all trees
#25	("dental prophylaxis"):ti,ab,kw
#26	("oral prophylaxis"):ti,ab,kw
#27	(root NEXT (plane* or planing)):ti,ab,kw
#28	MeSH descriptor: [Dental Devices, Home Care] this term only

#29	((Dental OR oral OR teeth OR tooth OR supragingival OR supra-gingival OR "supra gingival" OR subgingival OR sub-gingival OR "sub gingival") NEAR/5 (scaling or scaler* or curettage or curette*)):ti,ab,kw
#30	((periodontal OR supra-gingival OR supragingival OR sub-gingival OR subgingival OR "supra gingival" OR "sub gingival") NEXT debridement*):ti,ab,kw
#31	MeSH descriptor: [Subgingival Curettage] explode all trees
#32	MeSH descriptor: [Diagnosis, Oral] explode all trees
#33	(((intraoral OR intra-oral OR "intra oral" OR extraoral OR extra-oral OR "extra oral") NEAR/3 (check-up* OR checkup* OR "check up*" OR inspect* OR exam* OR attend* OR recall* OR visit* OR diagnos?s))):ti,ab,kw
#34	((dental OR oral OR teeth OR tooth OR "proximal surface*") NEAR/2 (radiograph* OR ex-ray OR xray OR ex-rays OR x-rays OR "x ray*" OR "ex ray*")):ti,ab,kw
#35	MeSH descriptor: [Oral Hygiene] explode all trees
#36	("oral hygiene"):ti,ab,kw
#37	(mouth NEAR/2 hygiene):ti,ab,kw
#38	(mouth NEAR/2 care):ti,ab,kw
#39	(dental NEAR/2 care):ti,ab,kw
#40	(care NEAR/2 teeth):ti,ab,kw
#41	(oral NEAR/2 care):ti,ab,kw
#42	("plaque control*"):ti,ab,kw
#43	(professional NEAR/1 "plaque* removal"):ti,ab,kw
#44	(PMPR):ti,ab,kw
#45	(((health NEAR/4 promot*) AND (dental OR teeth OR mouth OR periodont* OR gingiv* OR oral))):ti,ab,kw
#46	((health NEAR/3 awar*) AND (dental OR teeth OR mouth OR periodont* OR gingiv* OR oral)):ti,ab,kw
#47	((dental OR teeth OR mouth OR periodont* OR gingival OR oral) AND (instruct* OR advis* OR advic* OR educat* OR teach* OR train*)):ti,ab,kw
#48	MeSH descriptor: [Dental Care] this term only
#49	MeSH descriptor: [Comprehensive Health Care] this term only
#50	{OR #15-#49}
#51	#14 AND #50 in Trials

Dentistry and Oral Science Source EBSCOHost (date run 17 July 2021)

S1	TI periodontit* OR AB periodontit*
S2	TI "periodont* attachment loss" OR AB "periodont* attachment loss"
S3	TI periodontal N1 pocket* OR AB periodontal N1 pocket*
S4	TI ((bleed*) N3 (probe* OR probing)) OR AB ((bleed*) N3 (probe* OR probing))
S5	TI (alveolar N2 (loss* or atroph*)) OR AB (alveolar N2 (loss* or atroph*))
S6	TI ((periodont* or alveolar) N1 resorption*) OR AB ((periodont* or alveolar) N1 resorption*)
S7	S1 OR S2 OR S3 OR S4 OR S5 OR S6
S8	TI "supportive periodontal therap*" OR AB "supportive periodontal therap*"
S9	TI "supportive periodontal care" OR AB "supportive periodontal care"
S10	TI SPT OR AB SPT
S11	TI (periodont* or dentition or dental or tooth or teeth) N4 (maintenance or maintain* or posttreat* or post-treat* or prevent*) OR AB (periodont* or dentition or dental or tooth or teeth) N4 (maintenance or maintain* or posttreat* or post-treat* or prevent*)
S12	TI "recall maintenance*" OR AB "recall maintenance*"
S13	TI "preventive maintenance" OR AB "preventive maintenance"
S14	TI ((post surg* or postsurgic* or post-surgic* or patient*) W0 recall) OR AB ((post surg* or postsurgic* or post-surgic* or patient*) W0 recall)
S15	TI "dental prophylaxis" OR AB "dental prophylaxis"
S16	TI "oral prophylaxis" OR AB "oral prophylaxis"
S17	TI (root W0 (plane* or planing)) OR AB (root W0 (plane* or planing))
S18	TI ((dental or oral or teeth or tooth or supragingival or supra-gingival or subgingival or sub-gingival) N7 (scaling or scaler* or curettage or curette*)) OR AB ((dental or oral or teeth or tooth or supragingival or supra-gingival or subgingival or sub-gingival) N7 (scaling or scaler* or curettage or curette*))
S19	TI ((periodontal or supragingival or supra-gingival or sub-gingival or subgingival) N1 debridement*) OR AB ((periodontal or supragingival or supra-gingival or sub-gingival or subgingival) N1 debridement*)

S20	TI ((intraoral or intra-oral or extraoral or extra-oral) N4 (check-up* or checkup* or inspect* or exam* or attend* or recall* or visit* or diagnos#s)) OR AB ((intraoral or intra-oral or extraoral or extra-oral) N4 (check-up* or checkup* or inspect* or exam* or attend* or recall* or visit* or diagnos#s))
S21	TI ((dental or oral or teeth or tooth or "proximal surface*") N3 (radiograph* or ex-ray or xray or exrays or x-rays or x-ray or "ex rays")) OR AB ((dental or oral or teeth or tooth or "proximal surface*") N3 (radiograph* or ex-ray or xray or exrays or x-rays or x-ray or "ex rays"))
S22	TI "oral hygiene" OR AB "oral hygiene"
S23	TI mouth N2 hygiene OR AB mouth N2 hygiene
S24	TI mouth N3 care OR AB mouth N3 care
S25	TI dental N3 care OR AB dental N3 care
S26	TI care N3 teeth OR AB care N3 teeth
S27	TI oral N3 care AND AB oral N3 care
S28	TI "plaque control*" OR AB "plaque control*"
S29	TI professional N2 "plaque* removal" OR AB professional N2 "plaque* removal"
S30	TI PMPR OR AB PMPR
S31	TI (health N5 promot* AND (dental or teeth or mouth or periodont* or gingiv* or oral)) OR AB (health N5 promot* AND (dental or teeth or mouth or periodont* or gingiv* or oral))
S32	TI ("health awar*" AND (dental or teeth or mouth or periodont* or gingiv* or oral)) OR AB ("health awar*" AND (dental or teeth or mouth or periodont* or gingiv* or oral))
S33	TI ((dental or teeth or mouth or periodont* or gingival or oral) AND (instruct* or advis* or advic* or educat* or teach* or train*)) OR AB ((dental or teeth or mouth or periodont* or gingival or oral) AND (instruct* or advis* or advic* or educat* or teach* or train*))
S34	S8 OR S9 OR S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33
S35	S7 AND S34
S36	TI (rats or rat or animal or animals or mice or mouse or "in vitro") OR AB (rats or rat or animal or animals or mouse or mice or "in vitro")

S37	S35 NOT S36
S38	Narrow by Language: - English

CINAHL Plus EBSCOHost from 1937 to 17 July 2021

S1	(MH "Periodontitis+")
S2	(MM "Alveolar Bone Loss") OR (MM "Periodontal Attachment Loss")
S3	TI periodontit* OR AB periodontit*
S4	TI "periodont* attachment loss" OR AB "periodont* attachment loss"
S5	TI periodontal N1 pocket* OR AB periodontal N1 pocket*
S6	TI ((bleed*) N3 (probe* OR probing)) OR AB ((bleed*) N3 (probe* OR probing))
S7	TI (alveolar N2 (loss* or atroph*)) OR AB (alveolar N2 (loss* or atroph*))
S8	TI ((periodont* or alveolar) N1 resorption*) OR AB ((periodont* or alveolar) N1 resorption*)
S9	S1 OR S2 OR S3 OR S4 OR S5 OR S6 OR S7 OR S8
S10	TI "supportive periodontal therap*" OR AB "supportive periodontal therap*"
S11	TI "supportive periodontal care" OR AB "supportive periodontal care"
S12	TI SPT OR AB SPT
S13	TI (periodont* or dentition or dental or tooth or teeth) N4 (maintenance or maintain* or posttreat* or post-treat* or prevent*) OR AB (periodont* or dentition or dental or tooth or teeth) N4 (maintenance or maintain* or posttreat* or post-treat* or prevent*)
S14	TI "recall maintenance*" OR AB "recall maintenance*"
S15	TI "preventive maintenance" OR AB "preventive maintenance"
S16	TI ((post surg* or postsurgic* or post-surgic* or patient*) W0 recall) OR AB ((post surg* or postsurgic* or post-surgic* or patient*) W0 recall)
S17	(MH "Preventive Dentistry+")
S18	TI "dental prophylaxis" OR AB "dental prophylaxis"
S19	TI "oral prophylaxis" OR AB "oral prophylaxis"
S20	TI (root W0 (plane* or planing)) OR AB (root W0 (plane* or planing))
S21	TI ((dental or oral or teeth or tooth or supragingival or supra-gingival or sub-gingival or subgingival) N7 (scaling or scaler* or curettage or curette*)) OR

	AB ((dental or oral or teeth or tooth or supragingival or supra-gingival or sub-gingival or subgingival) N7 (scaling or scaler* or curettage or curette*))
S22	TI ((periodontal or supra-gingival or supragingival or sub-gingival or subgingival) N1 debridement*) OR AB ((periodontal or supragingival or supra-gingival or sub-gingival or subgingival) N1 debridement*)
S23	(MM "Diagnosis, Oral") OR (MM "Radiography, Dental") OR (MM "Radiography, Dental, Digital") OR (MM "Radiography, Panoramic")
S24	TI ((intraoral or intra-oral or extraoral or extra-oral) N4 (check-up* or checkup* or inspect* or exam* or attend* or recall* or visit* or diagnos#s)) OR AB ((intraoral or intra-oral or extraoral or extra-oral) N4 (check-up* or checkup* or inspect* or exam* or attend* or recall* or visit* or diagnos#s))
S25	TI ((dental or oral or teeth or tooth or "proximal surface*") N3 (radiograph* or ex-ray or xray or exrays or x-rays or "x ray" or "ex rays")) OR AB ((dental or oral or teeth or tooth or "proximal surface*") N3 (radiograph* or ex-ray or xray or " ex ray" or exrays or x-rays or "x ray" or "ex rays"))
S26	MH ("Oral Hygiene+")
S27	TI "oral hygiene" OR AB "oral hygiene"
S28	TI mouth N2 hygiene OR AB mouth N2 hygiene
S29	TI mouth N3 care OR AB mouth N3 care
S30	TI dental N3 care OR AB dental N3 care
S31	TI care N3 teeth OR AB care N3 teeth
S32	TI oral N3 care AND AB oral N3 care
S33	TI "plaque control*" OR AB "plaque control*"
S34	TI professional N2 "plaque* removal" OR AB professional N2 "plaque* removal"
S35	TI PMPR OR AB PMPR
S36	TI (health N5 promot* AND (dental or teeth or mouth or periodont* or gingiv* or oral)) OR AB (health N5 promot* AND (dental or teeth or mouth or periodont* or gingiv* or oral))
S37	TI ("health awar*" AND (dental or teeth or mouth or periodont* or gingiv* or oral)) OR AB ("health awar*" AND (dental or teeth or mouth or periodont* or gingiv* or oral))

S38	TI ((dental or teeth or mouth or periodont* or gingival or oral) AND (instruct* or advis* or advic* or educat* or teach* or train*)) OR AB ((dental or teeth or mouth or periodont* or gingival or oral) AND (instruct* or advis* or advic* or educat* or teach* or train*))
S39	(MM "Dental Care")
S40	(MM "Dental Health Education") OR (MM "Periodontal Examination")
S41	S10 OR S11 OR S12 OR S13 OR S14 OR S15 OR S16 OR S17 OR S18 OR S19 OR S20 OR S21 OR S22 OR S23 OR S24 OR S25 OR S26 OR S27 OR S28 OR S29 OR S30 OR S31 OR S32 OR S33 OR S34 OR S35 OR S36 OR S37 OR S38 OR S39 OR S40
S42	S9 AND S41
S43	MH animals+
S44	MH (animal studies)
S45	TI (animal model*)
S46	S43 OR S44 OR S45
S47	MH (human)
S48	S46 NOT S47
S49	S42 NOT S48
S50	Narrow S49 by Language: - English

Appendix H. Excluded Studies.

Reason for Exclusion	Publication
Insufficient follow up in supportive periodontal care	(Ramfjord et al., 1968, Ramfjord et al., 1973, Ramfjord et al., 1975, Aeschlimann et al., 1979, Axelsson and Lindhe, 1981a, Hakkarainen and Ainamo, 1982, Lindhe et al., 1982, Khoo and Newman, 1983, Badersten et al., 1984b, Lindhe and Liljenberg, 1984, Lindhe et al., 1984, Isidor and Karring, 1986, Wennstrom et al., 1986, Ramfjord et al., 1987, Needleman and Watts, 1989, Badersten et al., 1990, Renvert et al., 1990, Yukna and Shaklee, 1993, Joss et al., 1994, Cortellini et al., 1996, Dahlen et al., 1996, Renvert et al., 1996, Bostrom et al., 1998, Meinberg et al., 2001, Eickholz and Hausmann, 2002, Guarnelli et al., 2004, Sculean et al., 2004, Paquette, 2005, Preshaw et al., 2005, Hoffmann et al., 2006, Mengel et al., 2006, Gaspirc and Skaleric, 2007, Ozcelik et al., 2007, Bogren et al., 2008, Escribano et al., 2010, Paul et al., 2010, Saito et al., 2010, Cortellini et al., 2011, Costa et al., 2011, Shah and Kumar, 2011, Chen et al., 2012, Ratka-Kruger et al., 2012, Tonetti et al., 2012, Wong et al., 2012, Brauchle et al., 2013, Dori et al., 2013a, Delatola et al., 2014, Anyanechi et al., 2015, Hagi et al., 2015, Iwasaki et al., 2016, Goel and Baral, 2017, Preus et al., 2017b, Preus et al., 2017a, De Bruyckere et al.,

Reason for Exclusion	Publication
	2018, Lu et al., 2018, Nibali et al., 2018, Ramich et al., 2018, Eickholz et al., 2019, Nakao et al., 2020, Zuza et al., 2020)
Active periodontal therapy not presented as part of study	(Hirschfeld and Wasserman, 1978, Nyman and Lindhe, 1979, Jin et al., 1995, Wilson et al., 1997, Soder et al., 1999, Jenkins et al., 2000, Kamma and Baehni, 2003, Papantonopoulos, 2004, Guarnelli et al., 2010, Martin et al., 2010, Martin et al., 2011, Sugi et al., 2011, Mohd-Dom et al., 2014, 2015, Franke et al., 2015, Graetz et al., 2017, Costa et al., 2018, Sonnenschein et al., 2018, Rudiger et al., 2019)
No intervention	(Albandar, 1990, Aass et al., 1994, Beck et al., 1997, Bergstrom et al., 2000, Schatzle et al., 2004, Gatke et al., 2012, Appukuttan et al., 2016, Brignardello-Petersen, 2018a, Llanos et al., 2018)
Not periodontitis cases/ Mix of cases/ specific excluded population	(Valderhaug and Birkeland, 1976, Valderhaug, 1980, Axelsson et al., 1991, Valderhaug et al., 1993, Budtz-Jorgensen, 1995, Westfelt et al., 1996, Chen et al., 2001, Axelsson et al., 2004a, Petersson et al., 2006, Christan et al., 2007, Persson et al., 2007, Kim et al., 2013, Yu et al.,

Reason for Exclusion	Publication
	2016, Gomes et al., 2019, Zhang et al., 2020)
Not clinical study (systematic review, review, commentary, erratum)	(Ramfjord, 1981, Shick, 1981, Ramfjord et al., 1987, Ramfjord, 1990, Ramfjord, 1993, Nevins, 1996, Anonymous, 1998, Anonymous, 2003, Lang and Tonetti, 2003, Bonito et al., 2004, Gaunt et al., 2008a, Williams, 2008, Saxer, 2011, Ito et al., 2014a, Schwendicke et al., 2016, Brignardello-Petersen, 2017a, Albuquerque et al., 2018, Brignardello-Petersen, 2018b, Anupama et al., 2019, Brignardello-Petersen, 2019, Hodges, 2019, Pich, 2019, Zymperdikas et al., 2020)
Unable to obtain full text	(Sternig, 1985, Pollack, 1986, Abu el Fadl and el Refai, 1987, Hou et al., 1987, Günay, 1988, Itic and Serfaty, 1988, Chaves et al., 1990, Wilson, 1991, Ho et al., 1998, Pepelassi et al., 2005, P, 2013)
Retrospective	(Rams et al., 1985, Wilson et al., 1987, McGuire, 1991, Bragger et al., 1992, Wojcik et al., 1992, Efeoglu and Sandalli, 1996, McGuire and Nunn, 1996b, McGuire and Nunn, 1996a, Yukna and Yukna, 1997, Bader and Boyd, 1999, McGuire and Nunn, 1999, Tonetti et al., 2000, Meinberg et al., 2001, Moser et al., 2002, Cortellini and Tonetti, 2004, Chambrone and Chambrone, 2006, Carnevale et al., 2007b, Carnevale et al., 2007a,

Reason for Exclusion	Publication
	Eickholz et al., 2007, Faggion et al., 2007, Farina et al., 2007, Jansson and Norderyd, 2008, Matuliene et al., 2008, Pretzl et al., 2009, Graetz et al., 2011, Meyer-Baumer et al., 2013, Salvi et al., 2014, Ramseier et al., 2015, Dannewitz et al., 2016, Brignardello-Petersen, 2017b, Goh et al., 2018, Nibali et al., 2019, Saho et al., 2019, Cortellini et al., 2020a)
Case report/ series	(Heden and Wennstrom, 2006, Mros and Berglundh, 2010, Silvestri et al., 2011, Yanagishita et al., 2012, Komiya-Ito et al., 2013, Okuda et al., 2013, Carnio et al., 2015, Hu et al., 2015, Siqueira et al., 2015, Miao et al., 2016, Bhat et al., 2018, Clementini et al., 2018, Tobiska and Krastl, 2018, Guarnieri, 2019, Iorio-Siciliano et al., 2019)
Cross-sectional	(Ito et al., 2014b, Jansson et al., 2014, Lawal et al., 2015, Vaziri et al., 2016, Zhang et al., 2020)
Outcomes not relevant/ part of another study with longer follow-up	(Fleszar et al., 1980, Novaes et al., 1996, Nickles et al., 2009, 2015)

Appendix I. Focussed Question -1: Outcomes in included studies

Publication	Time point (months)	Outcomes		
		Tooth Loss	No. sites CAL loss ≥2 mm n (%)	Comments
Axelsson & Lindhe 1981	60	1.6† (Recall) 2.6† (Non-Recall)	NR	**Non-Recall**: SPC with general dentist (1/3). **Recall**: SPC 3monthly, Univ. program (2/3). **Reason(s) for extraction:** NR **Among sites with CAL loss:** Non-Recall: 44%= ≤1 mm, 55%=2-5 mm, 1%= 6 mm Recall: 99%= ≤1 mm, 1%= 2-5 mm **FMBS†:** BL: 7%(±4.8)(Recall); 4%(±2.7)(Non-Recall) Final: 2%(±4.0)(Recall); 55%(±23.0)(Non-Recall)
Becker et al. 2001	60	0	NR	**Teeth lost:** n=6 (5-12 years) **CAL change**: not reported from after APT

Publication	Time point (months)	Outcomes		
		Tooth Loss	No. sites CAL loss ≥2 mm n (%)	Comments
				GI†: BL: 0.28(±0.63)(SRP); 0.11±0.55(Oss); 0.20±0.47(MWF) Final: 0.56±0.91(SRP); 0.43±0.55(Oss); 0.54±0.67(MWF)
Buchmann et al. 2002			**Total: 64**	
	6		8 (10.6)	
	12	NR	11 (11.2)	
	24		7 (9.7)	
	36		12 (16.3)	
	48		9 (11.7)	
	60		17 (18.3)	
Cieplik et al. 2018	156	7 (15.9%)		**Tooth loss:** Controls (n=3), Test (n=4) **Reason for extraction:** non periodontal

Publication	Time point (months)	Outcomes		
		Tooth Loss	**No. sites CAL loss ≥2 mm n (%)**	**Comments**
Cortellini et al. 2017	240	**Total: 2 (4.9%)** MPPT = 0 (0%) GTR = 0 (0%) MWF = 2 (14%)	**Total: 26** MPPT = 5 (4 pts) GTR = 6 (5 pts) MWF = 15 (8pts)	**Reasons for extraction:** Periodontitis (non-responding) **Number smokers:** n=6 (2 each treatment group) **FMBS†:** BL: 7.1%± 2(MPPT); 6% ±2.71(GTR); 7.3%±2.8 (MWF) Final: 7.1%± 22(MPPT); 7.2 %±3(GTR); 7.2%±3 (MWF)
Cortellini et al. 2020	60	**Total: 5 (10.4%)** 2 (8%)	NR	**Reasons for extraction**: Unsuccessful regeneration (n=2), trauma

Publication	Time point (months)	Outcomes		
		Tooth Loss	No. sites CAL loss ≥2 mm n (%)	Comments
	120	3 (13%)		(n=1)
Crespi et al. 2011		NR	NR	CAL† by initial PPD at 6 months after APT (BL) and 180-month follow-up (final): **Initial PPD** **PPD 1-4 mm** BL: 3.49±0.91(MWF); 2.40±0.76(Laser) Final: 3.88±0.23 MWF); 2.78±0.65(Laser) **PPD 5-6mm** BL: 5.50±0.53(MWF); 2.86±2.43(Laser) Final: 5.74±0.21(MWF); 2.55±1.55(Laser) **PPD >6mm** BL: 7.29±0.93(MWF); 3.98±1.12(Laser) Final: 8.23±0.63(MWF); 3.61±1.11(Laser) **GI†:** BL: 0.47±0.59(MWF); 0.52±0.54(Laser) Final: 1.07±0.62(MWF); 1.10±0.54(Laser)

Publication	Time point (months)	Outcomes		
		Tooth Loss	**No. sites CAL loss ≥2 mm n (%)**	**Comments**
Dori et al. 2013	120	0	**Total: 5 (23%)** Xeno = 2 (18%) ß-TCP = 3 (27%)	**FMBS†:** BL: 11%(Xeno); 12%(ß-TCP) Final: 17%(Xeno); 19%(ß-TCP)
Hou et al. 1997		NR	NR	Change in CAL† reported between 3 months after APT (BL) and 72 months (Final) according to tooth surface: **PPD 1-3 mm** -0.02(B); -0.19(L); -0.15(M); -0.25(D) **PPD 4-6 mm** 0.16(B); 0.07(L); 0.14(M); 0.09(D) **PPD ≥7mm** -0.07(B); 0.07(L); 0.15(M); 0.08(D)
Kaldahl et al. 1996a	84	46 (+2 roots)	See Kaldahl et al. 1996b	**Reasons for extractions/amputation:** Periodontitis. Non periodontal extractions: 27 teeth (+5 root

Publication	Time point (months)	Outcomes		
		Tooth Loss	No. sites CAL loss ≥2 mm n (%)	Comments
				amputations)
Kaldahl et al. 1996b	84	See Kaldahl et al. 1996a	1.24%† incidence/year	**Breakdown site** = CAL loss ≥3 mm 75% = <1.99%† incidence/year 10% = >3.0%† incidence/year (all smokers)
Knowles et al. 1979		NR	NR	**CAL† change:**. Unable to extract exact values – readers are referred to Figure 12 of the original paper.

Publication	Time point (months)	Outcomes		
		Tooth Loss	No. sites CAL loss ≥2 mm n (%)	Comments
Loesche et al. 2002		**Total: 82**		**Reasons for extraction: periodontitis**
	13.2	26		
	43.2	24		13.2 months = 26 teeth extracted (17pts lost 1 tooth each, 3pts lost 2 teeth each, and 1pt lost 3 teeth)
	61. 2	32	NR	43.2 months = 24 teeth extracted (4pts lost 6 teeth each)
				61.2 months = 32 teeth extracted (4 pts lost 8 teeth each)
				No. teeth[†] requiring surgery OR extraction/ pt:
				13.2 months = 1.1
				43.2 months = 1.8
				61.2 months = 2.36

Publication	Time point (months)	Outcomes		
		Tooth Loss	**No. sites CAL loss ≥2 mm n (%)**	**Comments**
Loesche et al. 2005	76.8	NR	NR	**No. teeth[†] requiring surgery OR extraction/ pt:** 76.8 months = 1.5
Moder et al. 2012	84	**Total: 8 (17%)** GTR = 4 GTR+APC = 4	**Total: 14** GTR = 5 GTR+APC = 9	Teeth lost: n=8 in 6 pts CAL defined as ≤2 mm
Nygaard-Ostby et al. 2010	120	**Total: 2** GTR = 1 Control = 1	NR	**Reasons for extraction:** periodontal (control), unknown (GTR) **BOP[†] (site only):** BL: 84.6%±6.5(GTR); 42.3%±12.2(Control) Final: 42.3%±12.2(GTR); 34.6%±12.9(Control)

Publication	Time point (months)	Outcomes		
		Tooth Loss	No. sites CAL loss ≥2 mm n (%)	Comments
Orsini et al. 2008	120	0	NR	**CAL†:** reported from 6 months following APT (BL) and 120 months (final): BL: 5.0±0.8mm (control); 5.2±0.7mm (test) Final: 6.0±1.1mm (control); 6.4±1.4mm (test) **FMBS†:** BL: 35%(control); 36%(test) Final:39%(control); 38%(test)
Petsos et al. 2019	240	**Total: 7** OFD = 3 GTR = 4	**Total: 5** OFD = 2 GTR = 3	**Reasons for extraction**: mainly non-periodontal 7 teeth lost (1pt lost 3 teeth and was a smoker, 1 pt lost 2 teeth and was a smoker, and 2 pts lost 1 tooth each)

Publication	Time point (months)	Outcomes		
		Tooth Loss	No. sites CAL loss ≥2 mm n (%)	Comments
Pihlstrom et al. 1983		NR	NR	**CAL**[†] :reported in relation to BL and at time points of 6months, 1yr, 2yrs, 3yrs, 4yrs, 5.5yrs and 6.5yrs
Pihlstrom et al. 1984		**Total: 11** SRP = 5 MWF = 6		8 teeth extracted before APT finished
	27 2-60 61-77	2 (0.4%) 6 (1.3%) 3 (0.9%)		

Publication	Time point (months)	Outcomes		
		Tooth Loss	No. sites CAL loss ≥2 mm n (%)	Comments
Ramberg et al. 2001	144	1.72[†] (±1.0) (Test) 2.7[†a] (±3.7) (Control)	NR	**Annual CAL loss:** in both groups after the first year was small (between 0.07-0.11 mm) and similar between the two groups. **FMBS[†]:** BL: 24%±18(Test); 30%±19(Control) Final: 37%±12(Test); 32%±4(Control)
Rosling et al. 2001	144	1.9[†] (±2.2) (HSG) 0.3[†a] (±1.0) (NG)	NR	**HSG:** **-Reasons for extraction: Periodontitis** - 70% had >8 teeth with CAL loss ≥2mm - 34 (20%) exited study due to disease recurrence/progression

Publication	Time point (months)	Outcomes		
		Tooth Loss	No. sites CAL loss ≥2 mm n (%)	Comments
				NG: **-Reasons for extraction: non periodontal** - <10% had 8 teeth with CAL loss ≥2 mm - 7 (3%) exited study due to disease recurrence/ progression
Serino et al. 2001a	60	1.0†	NR	**Reasons for extraction: NR** **CAL loss†:** ≥0.2mm in 11 patients Cohort classed as 'downhill' patients due to recurrent disease following APT + 3yrs of APT. 12 out of 15 participants remaining were smokers. **FMBS†:** BL: 16%±18 Final: 15%±18

Publication	Time point (months)	Outcomes		
		Tooth Loss	No. sites CAL loss ≥2 mm n (%)	Comments
Serino et al. 2001b	156	1.6† (±1.7) (SRP) 0.6† (±1.1) (MWF)		**Reasons for extraction: NR** 4(14%) MWF & 8 (29%) SRP were exited from study due to disease progression **FMBS†:** BL: 18%±18(SRP); 16%%±19(MWF) Final: 30%±13(SRP); 31%±24(MWF)
	12-36		**PPD 0-3 mm:** SRP/ MWF 3.9% (±5.1)/ 2.1% (±3.5) **PPD≥6 mm:** SRP/ MWF 7.5% (±6.4)/ 5.3% (±6.1)	
	36-60		**PPD 0-3 mm:** SRP/ MWF 2.8% (±4.6)/ 0.4% (±1.2) **PPD≥6 mm:** SRP/ MWF 7.8% (±8.7)/ 4.0% (±5.6)	
	60-156		**PPD 0-3 mm:** SRP/ MWF 2.0% (±2.5)/ 2.1% (±4.3)	

Publication	Time point (months)	Outcomes		
		Tooth Loss	No. sites CAL loss ≥2 mm n (%)	Comments
			PPD≥6 mm: SRP/ MWF 2.9% (±8.2)/ 2.3% (±3.3)	

† = mean values per participant
[a] = statistically significant between groups

NR: not reported, SPC: supportive periodontal care, Univ.: university, FMBS: full mouth bleeding score, BL: baseline, CAL: clinical attachment level, APT: active phase of periodontal therapy, GI: gingival index, SRP: scaling and root planing, Oss: Osseous recontouring, MWF: modified Widman flap, MPPT: modified papilla preservation technique, GTR: guided tissue regeneration, FMBS: full mouth bleeding score, Xeno: xenograft, ß-TCP: beta tri-calcium phosphate, APC: autologous platelet concentrate, PPD: periodontal probing pocket depth, B: buccal, L: lingual, M: mesial, D: distal, n: number, pt: patient, BOP: bleeding on probing, pt: patient, OFD: open flap debridement, yr: year, HSG: highly susceptible group, NG: normal group

Appendix J. Focussed Question-2: Outcomes in Included Studies

Publication	Time point (months)	Outcomes			
		Tooth Loss	CAL & PPD change (mm)		Comments
			Test	Control	
Andere et al. 2022	12	NR	**CAL† gain:** 0.61 ±1.18 **PPD† reduction:** 1.02 ±1.02	 0.36 ±1.52 1.42 ±1.2	Test: 23 subjects; Control: 23 subjects Differences in CAL gain between test and control groups was not statistically significant. Control had statistically significant greater PPD reduction (p=0.001) compared to test at 12 months.
Angst et al. 2019	24	NR	**CAL† loss:** 0.1 mm **PPD† increase:** Initial PPD≥4 mm 0.17 Initial PPD≥5 mm 0.19	 0.09 mm 0.26 0.48	Test: 31 subjects; Control; 31 subjects Disease recurrence (No. of sites CAL loss ≥2 mm): **Initial PPD=4 mm** Test: n= 35 (11.6%), Control: n=28 (10.5%) **Initial PPD=5 mm** Test: n= 13 (16.3%), Control: n= 4 (8.3%) **Initial PPD≥6 mm**

Publication	Time point (months)	Outcomes			
		Tooth Loss	CAL & PPD change (mm)		Comments
			Test	Control	
					Test: n= 3 (10.7%), Control: n= 3 (30%) No benefit observed for test over control at 12 months.
Bogren et al. 2008	36	0.4† sites (Test) 0.7† sites (Control)	**CAL† gain:** 0.9 (95% CI 0.63-1.20) **PPD† reduction:** -1.2	 0.7 (95% CI 0.46-0.98) -1.1	Test: 63 subjects; Control: 65 subjects Reasons for extraction: NR 70 sites lost due to extraction (25 test, 45 control) BOP: **BL** – 51% (95% CI 43.9-57.5) Test; 56% (95% CI 50.1-63.0) Control **36 months** – 32% (95% CI 25.9-38.8) Test; 38% (95% CI 328.-44.2) Control No benefit observed for test over control at 12 months.

Publication	Time point (months)	Outcomes			
		Tooth Loss	CAL & PPD change (mm)		Comments
			Test	Control	
Costa et al. 2015	60	0.6† (RC) 1.8†a (IC) 0.3† (RC-NST) 0.8†a (RC-ST) 2.2† (IC-NST) 2.8†a (IC-ST)	**CAL† loss % of affected sites:** Initial PPD≥4-5 mm: 13.7±1.0 (RC-ST) Initial PPD≥6 mm: 14.7±1.2 (IC-ST)	 12.9±1.7 (RC-NST) 13.9±2.2 (IC-NST)	RC: 96 subjects; IC: 116 subjects Reasons for extraction: NR In both RC and IC groups, ST influenced greater tooth loss after 5 years. Disease recurrence – RC: 25 subjects (26.0%); IC: 42 (36.2%)[a] RC-NST: 13, RC-ST: 12, IC-NST: 17, IC-ST: 25 BOP: **BL** – 24.6±4.2% (RC); 27.8±6.1% (IC) **60 months** – 24.9±5.1% (RC); 32.8±6.9% (IC)
			PPD†% of affected sites: Initial PPD≥4-5mm: 2.9±2.9 (RC-ST) 4.2±3.5 (IC-ST) Initial PPD≥6 mm: 0.9±1.4 (RC-ST) 1.4±0.3 (IC-ST)	 3.2±3.1 (RC-NST) 4.4±3.8 (IC-NST) 1.1±1.4 (RC-NST) 1.6±0.4 (IC-NST)	

Publication	Time point (months)	Outcomes			
		Tooth Loss	CAL & PPD change (mm)		Comments
			Test	Control	
Jasa et al. 2020	12	1 (control)	**CAL† gain:** 1.75 ± 0.3 **PPD† reduction:** -2.29 ± 0.21	 2.20 ± 0.3 -2.39 ± 0.21	Test: 24 subjects, Control: 26 subjects Reason for extraction: Caries BOP reduction % (site level, between BL and 12M): Test: 25% (p=0.003), Control: 33.3% (p=0.01) No benefit observed for test over control at 12 months.
Jenkins et al. 2000	12	NR	**CAL† change (incl. 'loser' sites):** -0.04±0.18 (SS) **CAL† change (excl. 'loser' sites):** 0.11±0.20 (SS) **PPD† change (incl. 'loser' sites):** 0.37±0.15 (SS)	 -0.13±0.19 (CS) 0.20±0.18 (CS) 0.59±0.13(CS)	CS: 17 subjects; SS: 14 subjects 'Loser' sites (CAL loss ≥2mm): n=21(SS); n=21(CS) BOP (all sites): **BL** - 47±7% (CS); 48±0.06%(SS) **12 months** - 58±6% (CS); 56±6%(SS) No benefit observed for test over control at 12 months.

Publication	Time point (months)	Outcomes			
		Tooth Loss	CAL & PPD change (mm)		Comments
			Test	Control	
			PPD† change (excl. 'loser' sites):		
			0.45±0.18 (SS)	0.65±0.14 (CS)	
Killeen et al. 2018	24	3 (Test=1 Control=2)	**CAL† gain:** 0.8±0.9	1.0±0.7	Test: 27 subjects; Control: 28 subjects No benefit observed for test over control at 24 months.
			PPD† reduction: -0.8±0.9	-1.0±0.6	
Killeen et al. 2022	12	NR	**CAL† gain:** 1.9±0.3	1.0±0.3	Test: 27 subjects; Control: 23 subjects At 12months, the test group had statistically significant greater PPD reduction (p=0.007) and CAL gain (p=0.03) than the control group.
			PPD† reduction: -2.3±0.3	-1.3±0.3	
Lulic et al. 2008	12	0	**CAL† change:** -0.09±0.41	-0.20±0.61	Test: 5 subjects (39 sites); Control: 5 subjects (31 sites) BOP (test sites only): **BL** - 97% (test); 84%(control) **12 months** - 77% (test); 87%(control) No benefit observed for test over control at 12 months.
			PPD† reduction: -0.27±0.43	-0.07±0.61	

Publication	Time point (months)	Outcomes			
		Tooth Loss	CAL & PPD change (mm)		Comments
			Test	Control	
Mendez et al. 2021 *(*secondary analysis of *Angst et al. 2019)*	24	NR	See *Angst et al. 2019*		Test: 31 subjects; Control; 31 subjects OHIP-14 Minimally important difference: 4.19 33.9% (n=21) showed a change greater than the minimally important difference **OHIP-14 severity score:** BL: Test=7.67 (±9.27); control=6.51(±7.47) 24months: Test=5.03 (±6.79); control=4.16 (±4.78). Not statistically significant between groups (p=0.311). **OHIP-14 extent score:** BL: Test=0.87 (±1.63); control=0.48 (±0.99) 24months: Test=0.45 (±1.09); control=0.16 (±0.45). Not statistically significant between groups (p=0.064). **OHIP-14 prevalence score:** BL: Test=35.48 (±48.63); control=25.81 (±44.48)

Publication	Time point (months)	Outcomes			
		Tooth Loss	CAL & PPD change (mm)		Comments
			Test	Control	
					24months: Test=19.35 (±40.16); control=12.90 (±34.07). Not statistically significant between groups (p=0.079). Smokers and moderate oral hygiene (plaque >15%) displayed greater impacts on OHRQoL (higher risk of answering 'fairly often' or 'very often' at the last SPC visit.
Tonetti et al. 2012	12	NR	**PPD† change (relative to BL PPD):**		Test: 100 subjects; Control: 102 subjects

Publication	Time point (months)	Outcomes			
		Tooth Loss	CAL & PPD change (mm)		Comments
			Test	Control	
			Initial PPD 4 mm: -0.58	-0.57	'Loser' sites (CAL loss ≥2 mm): 15 subjects (7.5%) (excluded) – 8 (Test); 7(Control)
			Initial PPD 5 mm: -1.09	-0.98	Adverse events: 34 subjects with 56 events (Test) 49 subjects with 75 events (Control)
			Initial PPD 6 mm: -1.34	-1.26	No benefit observed for test over control at 12 months.
			Initial PPD 7 mm: -1.63	-1.70	
			Initial PPD >8 mm: -2.09	-2.23	

† = mean values per participant
[a] = statistically significant between groups

CAL: clinical attachment level, PPD: periodontal probing pocket depth, NR: not reported, 95% CI: 95% confidence interval, NST: non-surgical therapy, ST: surgical therapy, BOP: bleeding on probing, BL: baseline, RC: regular compliers, IC: irregular compliers, gp: group, SS: subgingival scaling group, CS: coronal scaling group

Appendix K. Newcastle-Ottawa Scale for assessing the quality of non-randomised, non-interventional studies.

Publication	**Selection (maximum = 3★)**	**Exposure/ Outcome (maximum = 3★)**
Axelsson & Lindhe 1981	★★★	★★
Becker et al. 2001	★★★	★★
Buchmann et al. 2002	★★★	★★
Cieplik et al. 2018	★★★	★★★
Cortellini et al. 2017	★★★	★★★
Cortellini et al. 2020	★★★	★★★
Crespi et al. 2011	★★★	★★
Dori et al. 2013	★★★	★★
Hou et al. 1997	★★★	★
Kaldahl et al. 1996a	★★★	★★★
Kaldahl et al. 1996b	★★★	★★★
Knowles et al. 1979	★★★	★★
Loesche et al. 2002	★★	★★
Loesche et al. 2005	★★	★★★
Moder et al. 2012	★★★	★★
Nygaard-Ostby et al. 2010	★★★	★★
Orsini et al. 2008	★★★	★★
Petsos et al. 2019	★★★	★★

Pihlstrom et al. 1983	★★★	★★★
Pihlstrom et al. 1984	★★★	★★★
Ramberg et al. 2001	★★★	★★★
Rosling et al. 2001	★★★	★★★
Serino et al. 2001a	★★	★★★
Serino et al. 2001b	★★★	★★★

Appendix L. Cochrane Risk of Bias Tool 2.0 for assessing the quality of randomised controlled trials.

	Randomisation	Deviation	Missing data	Outcome measurement	Selective reporting	**Overall risk**
Andere et al. 2022	Low	Low	Low	Low	Low	Low
Angst et al. 2019	Low	Low	Some Concern	Low	Low	Some Concern
Bogren et al. 2008	Low	Low	Low	Low	Some Concern	Some Concern
Jasa et al. 2020	Low	Some Concern	Low	Some Concern	Low	Some Concern
Killeen et al. 2018	Some Concern	High	High	Low	Low	High
Killeen et al. 2022	High	Some Concern	Low	Low	Low	High
Lulic et al. 2009	Some Concern	Low	Low	Low	Low	Some Concern
Mendez et al. 2021	Low	Low	Some Concern	Low	Low	Some Concern
Tonetti et al. 2012	Low	Low	Low	Low	Some Concern	Some Concern

Appendix M. Robins-I tool for assessing the quality of interventional non-randomised controlled trials/ prospective cohorts.

	Confounding	Selection of participants	Classification of interventions	Deviations from intended interventions	Missing data	Measurement of outcomes	Selection of the reported result	**Overall risk**
Costa et al. 2015	Serious	Low	Serious	Low	Low	Serious	NI	Serious
Jenkins et al. 2000	Moderate	Low	Serious	Low	NI	Serious	NI	Serious

NI = No Information