The Effect of Instrumentation Technique on the Outcome of Treatment for Periodontitis

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Table of Contents

Abstract

Objective: This study sought to investigate clinical, systemic inflammatory and patient-reported outcomes comparing non-surgical treatment for periodontal disease using exclusively hand instruments, ultrasonic instruments or a combination approach. Cost implications of periodontal treatment within a UK NHS Dental Hospital are described.

Methods: Fifty-five patients were treated between two studies (randomised controlled trial and cohort study) for generalised periodontitis using non-surgical periodontal therapy using hand instruments (HI), ultrasonic instruments (UI) or a combination approach (CI) with a 90 day follow up. Comparative analysis was carried out with respect to instrumentation technique at day 90. Success of treatment was objectively assessed against published criteria. Financial implications and patient reported outcomes of non-surgical periodontal therapy are explored by descriptive analyses.

Results: Non-surgical periodontal treatment was clinically effective across all instrumentation approaches at Day 90 follow up ($p<0.05$). Inter-group comparisons demonstrated no clinically significant differences in clinical or systemic inflammatory outcomes. UI required less time to complete treatment compared to HI, mean difference 21.51 minutes ($p<0.003$; 95% CI 9.22 to 34.62) Objective criteria of success demonstrated a lack of agreement in defining successful clinical endpoints. UI had least associated reprocessing and maintenance costs.

Conclusions: Clinical and systemic inflammatory outcomes were comparable between HI, UI and CI. Comparing HI and UI, UI had a shorter treatment time. UI was least costly on a recurring basis. Patients reported satisfaction with periodontal treatment.

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List of Tables

Chapter 3

Chapter 4

Chapter 5

Chapter 6

List of Figures

Chapter 2

Chapter 3

Chapter 4

Chapter 5

List of Abbreviations

NSPT: Non-surgical periodontal treatment

HI: Hand instrumentation

UI: Ultrasonic instrumentation

CI: Combination instrumentation

BOP: Bleeding on probing

CAL: Clinical attachment loss

PPD: Probing pocket depth

PPD≥5mm: Periodontal probing depth pockets of ≥5mm

PISA: Periodontal inflamed surface area

RCT: Randomised controlled trial

TNF alpha: Tumour necrosis factor alpha

IL-6: Interleukin 6

CRP: C-reactive protein

GLM: General linear modelling

SD: Standard deviation

NHS: National Health Service

List of Accompanying Material

Published manuscript within peer reviewed journal (*Journal of Clinical Periodontology*) outlining findings from randomised controlled trial – data utilised within current study.

The systemic inflammatory response following hand instrumentation versus ultrasonic instrumentation – A randomised controlled trial
Johnston *et al*.

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Associated publications currently in progress:

Mechanical biofilm disruption causes microbial and immunological shifts in periodontitis patients
W. Johnston, B. T. Rosier, A. Artacho, M. Paterson, K. M. Piela, C. Delaney, J. L. Brown, G. Ramage, A. Mira, S. Culshaw
Submitted (29/9/20) for peer review to *Nature Biofilms and Microbiomes*

Periodontal Instrumentation Technique – Clinical Outcomes and Financial Aspects
M Paterson, W Johnston, A Sherriff, S Culshaw
In progress – planned for submission to *British Dental Journal*

Chapter 1 – General Introduction

1.1 Introduction

Periodontitis is a chronic inflammatory disease, associated with the presence of bacteria, that affects the support tissues around the teeth (Periodontology, 2016) and is mediated and modulated by the host immune system (Cunningham *et al.*, 2014). The global economic burden of periodontitis is estimated at 54 billion US dollars per year (Listl *et al.*, 2015) which ranks periodontal disease within the top 10 of all (dental or non-dental) global diseases for economic burden (Jin *et al.*, 2016, Kassebaum *et al.*, 2014, Marcenes *et al.*, 2013). Modern understanding of periodontitis encompasses a complex, multifactorial model of non-linear disease initiation and progression (Socransky *et al.*, 1984). Periodontitis causes gingival inflammation, loss of connective tissue attachment and ultimately supporting alveolar bone – leading to tooth mobility and eventual tooth loss if left untreated. Ongoing periodontal disease (encompassing the disease processes of gingivitis and periodontitis) results in both a localised and systemic rise in multiple inflammatory mediators (Archana *et al.*, 2015). There is an emerging bidirectional relationship (Cunningham *et al.*, 2014) between systemic diseases and periodontitis. Multiple studies have revealed intriguing links between systemic diseases, the periodontal inflammatory process and treatment of periodontitis. Further data has emerged that implicates periodontal instrumentation in the promotion of systemic bacteraemia, with resultant effects upon the systemic inflammatory system (Kinane *et al.*, 2005, Zhang *et al.*, 2013, Horliana *et al.*, 2014). This bacteraemia, to a healthy patient may be inconsequential. However, to a medically co-morbid individual, such an increase in inflammatory markers could potentially have negative effects upon general health. The corner stone of effective periodontal treatment is non-surgical root surface instrumentation. Non-surgical periodontal therapy using ultrasonic scalers and/or hand instruments has proven effective in reducing microbial burden, resolving local inflammation and creating a clinical condition compatible with periodontal health (Keestra *et al.*, 2015). Side effects of non-surgical treatment include gingival recession and tooth sensitivity (Lang and Lindhe, 2015). Periodontal instrumentation may also result in bacteraemia and systemic inflammation. Within the context of an aging population, the proposed

links between periodontitis, systemic disease and systemic inflammation highlights a need to investigate the systemic effects of periodontal treatment.

1.2 Epidemiology of Periodontitis

Periodontal disease is one of the most common chronic conditions of the human population worldwide. The 2009 UK Adult Dental Health Survey demonstrated around 37% of the UK adult population suffer from moderate periodontitis, with 8% of the population having the advanced form of the disease. Worldwide, it is reported approximately 11% of adults suffer from severe periodontitis (Bernabe *et al.*, 2020). In order to gather and monitor epidemiologic data across multiple countries, the WHO developed and introduced the Community Periodontal Index (CPI) in 1982 (Ainamo *et al.*, 1982). This scale was applied to sextants of the dentition and categories (from 0-4) denoted the severity of the periodontal disease process. A CPI of 0 indicates gingival health with no bleeding on probing and no increased periodontal probing depths; 2 indicated gingival bleeding and presence of calculus; 3 indicated shallow periodontal pockets (4-5mm) and 4 indicated deep periodontal pockets (≥6mm). This assessment system later came under scrutiny (Baelum and Papapanou, 1996) due to its inability to yield a sufficiently detailed estimate of periodontal disease severity and its tendency to summarize periodontal disease at the subject level. The CPI scale later inspired the development of the Basic Periodontal Examination (BPE), developed by the British Society of Periodontology as a routine periodontal health screening tool, initially adopted in 1986 in the United Kingdom.

Periodontal disease prevalence is affected by multiple factors. Data demonstrates periodontal disease prevalence and severity affecting older age groups to a greater degree than younger populations (Petersen, 2003). A study (Drury *et al.*, 1999) examining data gathered during the US National Health and Nutrition Examination Survey (NHANES III) between the years 1988-1994 highlighted socioeconomic status and ethnicity as having statistically significant effects upon periodontal disease prevalence. 14,000+ subjects were assessed. Disparities in prevalence of gingivitis (ranging from 45.7% in high socioeconomic status to 63.4% in low socioeconomic status) and periodontal loss of attachment

of 4mm or more (20.6% in high socioeconomic status to 33.3% in low socioeconomic status) were found. An update to the NHANES study published in 2015 (Eke *et al.*, 2015) (which used the more accurate method of 6 point probing on each tooth) showed consistent evidence that periodontal disease occurred with comparative high frequency in low-income and older individuals, with an overall 46% of the US population affected by periodontal disease and prevalence varying two fold between low and high socioeconomic classes. A later 2013 study (Buchwald *et al.*, 2013) of a Pomeranian population of 2566 subjects corroborated these findings - low education and low income were statistically significant in relation to progression of mean clinical attachment loss ($p < 0.01$ and $p = 0.046$ respectively).

Further identified factors in the prevalence of periodontal disease are those of race and geographical location. Data from the aforementioned NHANES III study update identified periodontitis prevalence being highest in Hispanics (63.5%) and non-Hispanic blacks (59.1%) followed by non-Hispanic Asian Americans (50%) and lowest in non-Hispanic whites (40.8%) (Eke *et al.*, 2015). Further variation was shown in a Tanzanian population (Baelum *et al.*, 1986) with less than 35% of all surfaces assessed exhibiting loss of attachment ≥4mm and less than 10% of surfaces having attachment loss exceeding 6mm. A 2003 Swedish cross sectional survey, repeated over a period of 30 years, demonstrated 28% of subjects having less than one third of root length horizontal bone loss with 11% experiencing severe (more than one third of root length) alveolar bone loss (Hugoson *et al.*, 2008) and an evident trend for decreasing prevalence of periodontal disease over time – reaching its minimum at the last time point. More locally, the 2009 UK Adult Dental Health Survey identified only 17% of dentate adults had no evidence of periodontal disease in England, Wales and Northern Ireland (Steele *et al.*, 2012). One of the most impressive periodontal disease data libraries, grouped by geographic location, is the Periodontal Country Profiles database, held by the World Health Organisation, most recently updated in December 2017 (Organization., 2005. Accessed September 2019. Available from https://www5.dent.niigata-u.ac.jp/~prevent/perio/contents.html). From this database, it is reported that periodontal disease has an approximate prevalence (in 35-44 year olds) ranging from 60% in the USA, 75% in the UK to a

reported 28% in Brazil and approximately 10% in Saudi Arabia. This reported extreme variation in prevalence is potentially due to insufficient available data or may indeed be a true reflection of influence of geographic/race upon disease prevalence. Collectively, these data suggest notable differences in periodontal disease susceptibility between different populations across the globe. Such reported variations in prevalence of periodontal disease may be due to a variety of factors including: bias, varying classification methods of disease status, number of teeth examined and sample size discrepancies.

1.3 Aetiopathogenesis of Periodontitis

1.3.1 Pathogenesis

Gingivitis is a reversible condition, with negligible consequences to the periodontium (Axelsson and Lindhe, 1981a, Pihlstrom *et al.*, 2005). Gingivitis is a 'non-specific inflammatory condition that is the result of sustained plaque biofilm accumulation at and apical to the gingival margin'(Murakami *et al.*, 2018). Following accumulation of dental plaque around the cervical aspect of the tooth, changes within the gingival tissues are observed. In sequence: increased gingival crevicular fluid exudation; infiltration of gingival connective tissue with numerous macrophages and lymphocytes; followed by a predominance of plasma cells and finally collagen depletion has been observed (Lindhe *et al.*, 1980). Clinical signs of gingivitis include: redness, swelling, oedema, increased gingival crevicular exudate and bleeding on probing. Gingivitis has been identified to be a necessary pre-requisite for the development of periodontal disease through a variety of longitudinal studies. A classic study by Loe *et al* carried out on Sri Lankan tea workers (Loe *et al.*, 1986) identified three distinct patterns of periodontal disease – with all subjects that progressed to periodontal disease having evidence of gingivitis. Further studies (Ramseier *et al.*, 2017, Schatzle *et al.*, 2003, Clerehugh *et al.*, 1995) continued to consistently demonstrate sites developing periodontitis were preceded by clinical gingivitis. Interestingly, within a particular cohort of patients, gingivitis does not appear to progress to periodontitis – despite prolonged plaque accumulation and associated inflammation (Baelum *et al.*, 1986, Loe *et al.*,

1986). This phenomenon was foreseen by Lindhe's earlier studies in the beagle dog as progression to periodontitis was not consistent following ligature-induced-plaque-related gingivitis (Lindhe *et al.*, 1973). The collective conclusions of these studies would imply that plaque induced gingivitis alone is not sufficient to initiate the progression of destructive periodontitis – thus other factors must affect the condition (such as host related or environmental factors).

In approximately 80% of patients, untreated gingivitis will progress to destructive periodontal disease. Following on from the collagen depletion seen in the established gingivitis lesion (Page and Schroeder, 1976), the inflammatory cell infiltrate continues to develop and with apical migration of the junctional epithelium, the characteristic threshold of periodontitis is reached – the substitution of the junctional epithelium for pocket epithelium. An increase in the magnitude of the inflammatory cell infiltrate continues with concurrent loss of connective tissue and supporting alveolar bone. If left untreated in this state, the microbial community and inflammatory response will be maintained and develop (albeit at varying rates within populations (Baelum *et al.*, 1986))– with progressive mobility of the involved tooth and given time and left untreated, its eventual loss (Giargia and Lindhe, 1997).

1.3.2 Aetiology – Bacterial Plaque

Within seconds of performing oral hygiene, a layer of salivary proteins selectively adsorbs to enamel and oral mucosa to form a thin layer known as the salivary pellicle (Mandel, 1987). This layer is on average 17nm thick (Zhang *et al.*, 2016) and infers beneficial effects such as lubrication, nutrient decomposition and remineralization of dental hard tissues. This layer is understood to affect the charge of the surface, thus promoting bacterial accumulation and adhesion (Gibbons and Houte, 1975). Historic work (Ritz, 1967, Frank and Brendel, 1966) identified S*treptococci* strains (facultative Gram-positive cocci) as being early colonisers upon the acquired pellicle, thus initiating the formation of dental plaque. This theory was later corroborated by work by Lai and Listgarten who found a strain of *Streptococcus* had directly attached to the salivary pellicle at the base of the developing dental plaque (Lai

et al., 1975) and a distinct columnar arrangement was evident in supragingival plaque (Listgarten *et al.*, 1975). Modern techniques have established each site on a tooth with plaque accumulation houses approximately 30 different species of bacteria (Aas *et al.*, 2005), with an individual having over 400 species residing within the periodontal tissues (Dewhirst *et al.*, 2010b). It is thought approximately one third of bacterial phylotypes within the oral cavity are still to be cultured and identified (Thompson *et al.*, 2015).

Dental plaque itself is defined as a 'community of microorganisms found on a tooth surface, embedded in a matrix of polymers of host and bacterial origin' (Marsh, 2004). The formation of a biofilm community infers numerous benefits to the bacteria within, compared to existence as a single bacterium. Firstly, members are less susceptible to destruction by antimicrobial agents. Communication and cooperation between micro-organisms is facilitated through Quorum Sensing – the regulation of gene expression through accumulation of signalling compounds that mediate intercellular communications (Solano *et al.*, 2014). This process aids regulation of bacterial populations and sharing of genetic data, ensuring promotion of certain species to propagate the community. Biofilms are therefore well organised, physically attached structures comprised of potentially disease-causing bacteria. Thus, effective treatments for periodontal disease focus on the removal of the source of pathogenic bacteria – the biofilm.

Following the discovery of early colonisers adhering to the tooth surface, it was later confirmed that progression of the bacterial community is reliant upon bacteria-bacteria adhesion mechanisms (Vickerman and Jones, 1995). As more species of bacteria join the community, it is believed anaerobic conditions eventually predominate. The community develops towards one less conducive to periodontal health with distinct compositional variations in the members of the bacterial community (Tanner *et al.*, 1979, Slots, 1977). This occurs concurrently with the formation of a deepened periodontal pocket and the subgingival bacterial niche. As quantity of bacteria increases, so does severity of inflammation and periodontal pocket formation. This led to the popular theory of the 'non-specific plaque hypothesis' (Theilade, 1986) – with no acute

discrimination between specific bacterial organisms in the disease process and the belief volume of plaque alone was the most significant aetiological factor in periodontal disease initiation and progression.

Continued development within the subgingival environment occurs through a process of successive adhesion of groups of micro-organisms - with associations with each other and the ability to promote the adhesion of the subsequent micro-organism group. These associations were quantified by Socransky within 'bacterial complexes' (Socransky *et al.*, 1998). In this study, over 13,000 subgingival plaque samples were analysed and complexes of bacteria that were found in co-existence were assigned colours – green, purple, yellow, orange and red. Bacteria in the red (*Porphyromonas Gingivalis, Tannerella Forsythia and Treponema Denticola)* and orange complexes had strong relationships with increasing periodontal pocket depths and bleeding on probing. Furthermore, sites with no bacteria from the red complex showed evidence of the shallowest mean pocket depth compared to sites with all three red complex bacteria showing the deepest pockets. These findings question the theory of the 'non-specific plaque hypothesis', being more in favour of the 'specific plaque hypothesis' (Loesche, 1992) - the assumption that the presence of specific bacteria is indicative of disease state.

The 'specific plaque hypothesis' has evolved over recent years, as anomalies in periodontal microbiology became apparent that could not be explained with this model. Firstly, the red complex bacteria *Porphyromonas gingivalis* has been shown to be present in cases of oral health (Ximenez-Fyvie *et al.*, 2000, Diaz *et al.*, 2006), albeit in relatively low numbers – thus casting doubt on the hypothesis of 'red complex' bacteria being exclusive to diseased sites. Newly recognised micro-organisms, beyond that of the 'red complex', have shown very robust association with disease (Griffen *et al.*, 2012). Modern methods of 16S PCR amplification have also prompted questioning of the assumption of gram-negative bacteria predominating in periodontal disease by demonstrating gram-positive anaerobic cocci *Peptostreptococci* species in far greater numbers than those of gram-negative anaerobes commonly associated with periodontal disease (Kumar *et al.*, 2005, Dewhirst *et al.*, 2010a). It is therefore becoming more

compelling to consider an overall change in the pre-existing microbiome as part of a series of processes in the initiation and progression of periodontitis. These concepts were encapsulated in the 'ecological plaque hypothesis' – coined by Marsh in 1994 (Marsh, 1994). Specifically, this theory discusses changes in the environment (such as pH, temperature, osmotic pressure and availability of nutrients) resulting in enhanced expression of virulence factors from particular putative pathogens, to the detriment of competing bacterial species. Coupled with an aberrant host response, this could help explain the pathogenesis of periodontitis. In the contemporary literature, the term 'dysbiosis' has been used to allude to such changes in resident microorganism communities, leading to a relative imbalance with associated disease initiation.

A recent theory of periodontal disease progression is the 'keystone pathogen theory' first described by Hajishengallis (Hajishengallis *et al.*, 2012). This theory discusses the concept of the presence of certain microorganisms (specifically in low numbers) causing disproportionate effects within the microbiome leading to subsequent initiation and propagation of periodontal disease. Specifically, it is suggested that *P. gingivalis* may be a 'keystone pathogen' due to its ability to both subvert and alter the innate immune response – leading to significant environmental change and alteration of growth and development of the biofilm as a whole (Hajishengallis *et al.*, 2012) within a murine model. Interestingly, (again within a murine model) this same author has shown that even a small number of *P. gingivalis* inoculation alone is capable of inducing periodontitis through a significant 'growth enhancing effect' in an otherwise healthy commensal oral microflora. This particular study also provided further evidence of the importance of the complement pathway in periodontitis disease development – specifically C3a and C5a (Hajishengallis *et al.*, 2011) and the ability of *P. gingivalis* to modulate this mechanism at the expense of leukocyte killing capacity. Periodontitis associated bacteria express numerous virulence factors: leukotoxin production, collagenases, endotoxin and induction of cytokine production from macrophages, among others (Haffajee and Socransky, 1994) that have been shown to cause both direct and indirect damage to the periodontal tissues.

1.3.3 Aetiology – Host response

It has been argued that the host inflammatory response is both significant and instrumental in the initiation and progression of periodontal disease.

The innate immune response includes physical barriers to bacterial infection including junctional epithelium, activation of the complement cascade (which contributes to both innate and adaptive immune responses), migration of leukocytes and phagocytosis. Specific regions identified with leukocyte infiltration include the junctional epithelium and the adjacent connective tissues (Zadeh *et al.*, 1999). It has been shown that there is a constant level of 'immune surveillance' present in the periodontium – even in apparent clinical health (Brecx *et al.*, 1987). Bacterial biofilms present in periodontal disease are resistant to the process of phagocytosis (Thurlow *et al.*, 2011, Leid *et al.*, 2005). Furthermore, the biofilm also reduces interaction of bacteria with antigen presenting cells, thus reducing the potential efficacy of the adaptive immune response (Ebersole *et al.*, 2017). Initial inflammation is dominated by neutrophils, with macrophages increasing in numbers after 24-48 hours (Ali *et al.*, 2011). In an apparently frustrated attempt to address the bacterial biofilm, neutrophils perform 'netosis', with the release of elastases, hypochlorous acid and cathepsins. These are toxic to both bacterial and host cells of the periodontium. Of note, cathepsin K is particularly efficient in destruction of bone (Wen *et al.*, 2016). Macrophages also play a key role and recognise bacterial components through their Toll-like receptors, which can trigger the innate response and bridge the gap between adaptive and innate immune responses. Macrophages can phagocytose bacteria and then through antigen processing and presentation activate antigen specific T cells. The activated T helper cells provide assistance to B cells to generate specific antibodies (Albandar *et al.*, 2001). These antibodies have a variety of functions including opsonization and occupation of the specific pathogen's active receptor (Xynogala *et al.*, 2009). Analysing antibody production (for example IgG levels specific to certain pathogens) can provide evidence as to which microorganisms are responsible for the host reaction. This is achievable by immune-

checkerboard methods and have shown promise in linking clinical signs of disease with specific periodontal pathogens (Offenbacher *et al.*, 2008).

Following the immune and inflammatory responses, loss of connective tissue and periodontal tissue destruction is the culmination of a variety of processes, still under investigation which include: inadvertent destruction of connective tissue by polymorphonuclear leukocyte enzyme release; lipopolysaccharide directly stimulating osteoclastic activity (Lino and Hopps, 1984); cytokine promotion of tissue destruction by various means (Graves, 2008) and the action of matrix metalloproteinases (Nagase, 1997), released from a variety of cell types.

Alongside the local immune response, a simultaneous systemic inflammatory response is evident in periodontitis. A reliable, albeit nonspecific systemic marker of the acute phase of the inflammatory response is that of C-reactive protein (CRP). CRP is a plasma protein whose presence within serum is indicative of ongoing inflammation (Black *et al.*, 2004). Elevated CRP (Podzimek *et al.*, 2015) associates with the severity of periodontal disease, with highest levels found in patents with the aggressive form of periodontitis. A mean CRP of 2.28mg/L was identified in an aggressive periodontitis group studied. This level is in keeping with similar studies within the literature (Salzberg *et al.*, 2006, Gani *et al.*, 2009). Interestingly, it also reported that pre-treatment CRP levels within periodontitis affected populations differ according to ethnicity. This is evidenced in the mean values of CRP ranging from 1.1mg/L within a Caucasian American population (Salzberg *et al.*, 2006) to as high as 7.49mg/l within an Indian population (Chopra *et al.*, 2012). From a clinical perspective, bleeding on probing index has been shown to be a more reliable predictor of CRP levels compared to pocket depth index in the studied population. The consensus finding within the literature is of patients with more clinically severe periodontitis presenting with increased serum levels of CRP, compared to both unaffected control populations and patients with less severe periodontal disease (Gomes-Filho *et al.*, 2011, Ebersole *et al.*, 1997, Bansal *et al.*, 2014, Kumar *et al.*, 2013).

1.3.4 Factors Influencing Aetiology of Periodontitis

Alongside the microbiome and host response, smoking and diabetes significantly impact periodontitis. It has been established that subjects who smoke have deeper mean probing depths (Bergstrom and Eliasson, 1987), a greater degree of attachment loss (Haffajee and Socransky, 2001), higher levels of loss of supporting alveolar bone (Bergstrom *et al.*, 1991, Baljoon, 2005), more tooth loss (Mai *et al.*, 2013), more involvement of furcation regions (Mullally and Linden, 1996) and as a result of vasoconstriction – less gingivitis and bleeding on probing (Preber and Bergstrom, 1986, Haffajee and Socransky, 2001). A contemporary systematic review (Leite *et al.*, 2018) revealed a categorically increased risk for developing periodontitis of between 1.3 and 3.0 (relative risk) for patients who smoke. A dose-dependant effect has been reported (Bergstrom *et al.*, 2000). Tobacco smoking is therefore a highly significant confounder for the initiation and progression of periodontal disease.

Diabetic control has been implicated in the magnitude of the periodontal disease process. Diabetes is a significant factor in accelerated loss of clinical attachment (Grossi and Genco, 1998, Taylor *et al.*, 1996, Salvi *et al.*, 2008), independent of other risk factors for periodontal disease. Furthermore, diabetic control (as measured by HbA1c) is of importance – poor diabetic control is associated with both higher bleeding on probing scores and number of pockets ≥5mm (Lim *et al.*, 2007). The specific causative pathways explaining this relationship are currently under investigation. There is now emerging evidence of a 'two-way' relationship between diabetes and periodontitis. Besides the accepted relationship between poor diabetic control and periodontitis severity, it has been suggested the periodontitis disease process itself may negatively affect diabetic control (Preshaw *et al.*, 2012, Taylor, 2001, D'aiuto *et al.*, 2018).

1.4 Measuring Periodontal Health and Disease

Within a clinical context, periodontal disease is detected and diagnosed initially by periodontal probing. As periodontal disease progresses, apical migration of junctional epithelium results in formation of a 'periodontal pocket' which is

detectable by manual probing of the region. Periodontal probing is performed by placing the end of the probe in the gingival sulcus and applying 0.2N-0.5N of force in an apical direction, until the probe meets resistance. With increased severity of periodontal disease, an increase in periodontal probing depth is typically observed. This is a result of physical migration of the base of the pocket epithelium but also a reduction in tissue resistance as connective tissue is lost in late stage periodontal disease (Caton *et al.*, 1981). Probing depth and the extent of tissue penetration has been shown to be related to 'thickness of probe, pressure applied, contour of the tooth surface, degree of inflammatory cell infiltrate and accompanying loss of collagen fibres' (Listgarten, 1980). Therefore, inherent inaccuracies and error with this method of assessment have been noted (Grossi *et al.*, 1996). This prompted the development of an electronic probe capable of applying a constant force. Unfortunately this technology was demonstrated to suffer from error in a systematic review (Silva-Boghossian *et al.*, 2008). Thus, it is essential for robust training to be provided in periodontal probing techniques to ensure reliability in probing measurements (Hill *et al.*, 2006) and an error of 1mm in probing depth (either overestimation or underestimation) has been widely accepted by the periodontal scientific community.

To combine the multiple clinical parameters of periodontal disease progression into a single entity and estimate the inflammatory burden of periodontitis, Nesse *et al* (Nesse *et al.*, 2008) introduced the concept of 'PISA' (Periodontal Inflamed Surface Area) – following on from ALSA (Attachment Loss Surface Area) work by Hujoel (Hujoel *et al.*, 2001). This single value aims to provide an indicator of the volume of inflamed tissue involved in periodontitis and offer a clinically relevant combined indicator of disease status. Calculating PISA is a seven-step process and involves reference to root surface area, clinical attachment loss, bleeding on probing and recession measurements. PISA is calculated for each tooth in turn and then combined to provide an overall value for inflamed surface area for the whole mouth. Values for PISA for a periodontally healthy patient and a patient with generalised severe periodontal disease reside around 28.6mm^2 and 3704.2mm^2 respectively (Nesse *et al.*, 2008). Values of PISA have been shown to be a strong predictor of periodontitis

presence – with a sensitivity of 98% and a specificity of 100% (Leira *et al.*, 2018). Further, lower quality evidence corroborates these finding with a post-hoc analysis of another study's subject cohort (Park *et al.*, 2017). Association between PISA and cytokine concentration in gingival crevicular fluid was observed in a convenience sample of a small case control study (Govindarajan *et al.*, 2015). Further well-designed trials would strengthen the reliability of PISA as a measurement tool for both periodontal disease and an indicator of periodontitis' contribution to systemic inflammatory burden.

There are limitations of PISA aside from accepted measurement errors of CAL and PPD. Integral values for root surface area were derived from a meta-analysis of average root surface areas combining 22 studies – analysing 4730 root surface area measurements (Hujoel, 1994). In this study, significant heterogeneity between studies was noted and a variety of biases were suspected. For example, 'non-normal' teeth (ie fused roots) were excluded in some studies and multiple sources of potential measurement error in root surface area estimation were present. Therefore, validity of a meta-analysis of these measurements could legitimately be questioned. Extrapolating this data into the quantification of PISA may therefore be flawed and misleading. A further potential issue with PISA is that inflammatory infiltrate present around a tooth suffering periodontal disease will inevitably extend further than the immediate area of the root surface (Lang and Bartold, 2018). This therefore may lead to an underestimation of the actual inflamed volume of tissue. Another limitation of PISA relates to patients who smoke. The calculation of PISA includes taking account of bleeding on probing values, which may partially be masked in patients who smoke (Bergstrom and Eliasson, 1987) thus affecting PISA values. However, smoking status is shown to positively correlate with overall PISA value (Park *et al.*, 2017). Finally, cases with gingival overgrowth prove challenging for PISA calculation – as noted by the authors (Nesse *et al.*, 2008). Interestingly, values for PISA are also notably absent in the most recent classification of periodontal disease (Papapanou *et al.*, 2018).

As a supplement to clinical examination of the periodontal tissues, radiographs are a valuable detection method of the periodontal disease process. It has been

shown that specific features of diagnostic interest such as furcation involvement, periodontal ligament space widening, percentage of remaining bone support and periapical periodontitis are only evident to the clinician through radiographic examination (Tugnait *et al.*, 2000). The diagnosis of periodontitis is primarily by clinical examination and probing; however, radiographs serve as a very useful adjunct for guiding periodontal treatment planning decisions (Corbet *et al.*, 2009).

1.5 Periodontal Treatment Techniques

Fundamentally, the treatment for periodontitis relates to risk factor control and to the reduction of bacterial load within the oral cavity. The goal being to reduce the microbial burden both quantitatively and qualitatively to a level more conducive to health. Self-performed plaque control by the patient is an integral aspect of maintaining periodontal health which underpins all theories of management of periodontal disease (Lindhe *et al.*, 1984). Non-surgical periodontal therapy using ultrasonic scalers and/or hand instruments has proven effective in reducing microbial burden, resolving local inflammation and creating a clinical condition compatible with periodontal health (Keestra *et al.*, 2015). Further therapies exist within the literature including: subgingival irrigation (Greenstein, 1987), host modulation therapy (Oringer, 2002), antimicrobial therapy (Slots and Rams, 1990) and local antimicrobial therapies (Kinane, 2000). The modality with the largest volume of compelling evidence for effective outcomes remains that of non-surgical periodontal therapy using ultrasonic scalers and/or hand instruments (Cobb, 1996). The fact that success of periodontal therapy hinges on removal of deposits from the root surface underpins the effectiveness of mechanical means of deposit removal (Lindhe *et al.*, 1982, Badersten *et al.*, 1981).

In the historic literature, an objective of non-surgical periodontal therapy was that of ‘scaling and root planing’. This consisted of using principally hand instruments, with relatively significant force, to remove all subgingival calculus and ‘contaminated root cementum’ – leaving a ‘glass-like’ smooth root surface. This technique was practiced widely until research into endotoxin and bacterial

biproduct adherence to root surface surfaced. An initial in vitro study (Nakib *et al.*, 1982) demonstrated endotoxin on extracted teeth showed minimal penetration into dentine/cementum and was very loosely adherent –casting doubt on the previously held belief aggressive root planing was a requirement for successful therapy. A subsequent in *vivo* study (Mombelli *et al.*, 1995) confirmed successful clinical outcomes from non-surgical periodontal therapy could be obtained by avoiding aggressive root planing and only incomplete calculus removal. A further study demonstrated favourable cellular attachment to disinfected dental calculus (Listgarten and Ellegaard, 1973). Therefore, it has now been established that calculus is a plaque retentive factor however its complete removal is not necessary to achieve favourable outcomes, similarly, aggressive root planing with the intention of removal of root cementum is not required for favourable outcomes. Complete removal of calculus in pockets >5mm is uncommon, even in specialist hands (Brayer *et al.*, 1989). However small deposits of residual calculus have been shown not to negatively affect success rates of non-surgical periodontal treatment (Brayer *et al.*, 1989, Waerhaug, 1978).

1.5.1 Hand Instrumentation

Hand instrumentation for the treatment of periodontal disease consists of mechanically removing plaque and calculus deposits from the root surface, located within a periodontal pocket, using a specially designed curette. Advantages of hand instrumentation conventionally include: greater tactile feedback, no production of aerosols and close adaptation to specific sites. Suggested limitations of hand instrumentation include the requirements for regular instrument sharpening (Rees *et al.*, 1999), operator fatigue, greater treatment time and potential trauma to adjacent soft tissues. A wide body of evidence confirms favourable outcomes in relation to resolution of clinical parameters of periodontal disease for hand instrumentation (Badersten *et al.*, 1987, Ramfjord *et al.*, 1987, Lindhe *et al.*, 1984, Kaldahl *et al.*, 1996). There is also evidence that hand instruments may be effective as a final technique, following use of powered instruments, in order to achieve the smoothest root surface possible (Ruppert *et al.*, 2002).

1.5.2 Ultrasonic Instrumentation

Ultrasonic instrumentation is a subset of 'powered instrumentation techniques' and relate to the removal of plaque and calculus from the root surface using a rapidly vibrating metallic tip connected to a water irrigation system (water may be substituted for a variety of solutions) to keep the tip cool and flush debris from the operation site. There are two categories of ultrasonic scaler – piezoelectric and magnetostrictive. There is currently no evidence supporting superior clinical results of one type of ultrasonic scaler. It has been reported that piezoelectric devices cause a greater degree of damage to the root surface, compared to magnetostrictive (Busslinger *et al.*, 2001). Purported advantages of ultrasonic instrumentation include: acoustic streaming, less damage to root surface, microcavitation, flushing effects, better access to furcations (Clifford *et al.*, 1999) and improved operator comfort (Obeid *et al.*, 2004). Limitations of ultrasonic scalers include: production of aerosol, less tactile feedback and patient sensitivity from water spray. Technology within the field of ultrasonic instrumentation has developed through introduction of specialised tip designs (which aid in access to furcations or deep, narrow pockets) and operator comfort through patented on/off procedures through the use of a wireless foot pedal.

1.5.3 Hand Instrumentation vs Ultrasonic Instrumentation

Hand instrumentation and ultrasonic instrumentation have been compared through a variety of measures. Numerous studies have demonstrated equal efficacy in probing depth reduction, clinical attachment gain (Obeid *et al.*, 2004, Krishna and De Stefano, 2016), bleeding on probing reduction (Badersten *et al.*, 1981, Oosterwaal *et al.*, 1987), plaque removal ability (Thornton and Garnick, 1982) and reduction of red complex bacteria (Ioannou *et al.*, 2009). Superiority of ultrasonic scalers has been suggested in the treatment of furcations (Leon and Vogel, 1987) in an in vivo study of 33 furcation involved molar teeth – in particular Class II and Class III furcations showed superior outcomes with the use of ultrasonic instrumentation. The most recent

systematic review of the topic of efficacy of ultrasonics compared to hand instruments (Tunkel *et al.*, 2002) analysed 27 articles and reported no significant differences between ultrasonic and manual instrumentation techniques relating to clinical parameters of success for periodontal treatment or frequency of adverse effects. Meta-analysis was not possible due to heterogeneity of studies. A significant finding was of ultrasonic treatment taking less time than hand instrumentation (P=0.0002, 95% CI 0.39-1.37). The conclusion of this review stated 'the available data do not indicate a difference between ultrasonic/sonic and manual debridement in the treatment of chronic periodontitis for single-rooted teeth; however, the evidence for this is not very strong.' The authors suggested a need for further research into the efficacy of ultrasonics particularly in multirooted teeth. Therefore, current evidence would suggest that either hand instruments or ultrasonic instruments might effectively be used for non-surgical periodontal treatment. In reality, many operators use a combination of both.

1.6 Defining Success In Periodontal Treatment

Determining absolute success following non-surgical periodontal therapy can be a challenging endeavour. A variety of clinical outcome measures are reported, including changes in plaque percentage, bleeding on probing, periodontal probing depth and clinical attachment level. Each of these measures are usually initially evaluated three months post non-surgical therapy (Cobb, 1996). Conclusions can then be inferred as to the success or failure of therapy. It is important to note that any improvements in the patient's periodontal state can soon be reversed within a few weeks if self-performed plaque control becomes inadequate (Magnusson *et al.*, 1984).

There are challenges in defining success at a patient level, and further challenges when considering success at individual sites. Differences in probing attachment levels may also reflect changes in the inflammatory status and resistance to probing at the base of the pocket rather than true connective tissue loss or gain following therapy (Lindhe *et al.*, 1982). Moreover, limited reproducibility in probing measurements can adversely affect data. At an

individual site, bleeding on probing is a clinical indicator for active inflammation and is a reflection of decrease in collagen density and fragility of blood vessels (Polson *et al.*, 1981, Greenstein *et al.*, 1981). Although multiple studies report bleeding on probing as a relatively good predictor of future attachment loss (Badersten *et al.*, 1990, Lang *et al.*, 1986), others note the limitations of bleeding on probing as a predictor of future attachment loss (Haffajee *et al.*, 1983, Goodson, 1986). Further research has concluded that bleeding on probing has a weak correlation with future attachment loss and should be used as a 'criterion for stability rather than using as a predictor of disease activity' (Cobb, 2002, Lang *et al.*, 1986). Mean reduction in bleeding on probing percentage reported in a recent review of the literature following non-surgical periodontal therapy was that of approximately 45% (Cobb, 2002).

Periodontal probing depth has been identified as a particular strong indicator for determining further disease progression potential (Badersten *et al.*, 1987, Zimmermann *et al.*, 2015) and forms the basis of several historical and current classifications of periodontitis (Papapanou *et al.*, 2018). A common finding in assessment of pocket depth reduction is that of grouping pockets into three categories for assessment: 1-3 mm, 4-6 mm and >6 mm. Each of these categories can be expected to respond to non-surgical therapy with an approximate reduction in probing depth of 0.4 mm ± 0.2 mm, 2.0 mm ± 0.4 mm, 2.6 mm ± 1.0 mm (at 12 months) respectively (Heitz-Mayfield *et al.*, 2002). The response to non-surgical therapy is lessened when multi-rooted teeth (Loos *et al.*, 1989), including those with furcation involvement are treated by non-surgical (Badersten *et al.*, 1987, Loos *et al.*, 1989) or surgical means (Pihlstrom *et al.*, 1984). These findings illustrate the inherent difficulties in instrumenting the complex anatomy of multi-rooted teeth.

Defining criteria for 'success' in relation to periodontal therapy can also prove challenging. Success can be defined at site level, or at whole patient 'case' level. The number of successfully treated sites is likely to be higher than the number of successfully treated cases (Lundgren *et al.*, 2001). It has been suggested different success criteria should be applied to patients with differing levels of compliance, observed local disease resistance and value of the tooth

for the remaining dentition (Lundgren *et al.*, 2001). Lindhe (Lindhe *et al.*, 1982) developed a definition of 'clinically successful non-surgical periodontal therapy' as 'resolution of gingivitis and reduction of sites with deep pockets (>4mm probing depth). This definition however is perhaps deliberately vague, as it is recognised that not all patients respond predictably to periodontal therapy. A 2001 study (Lundgren *et al.*, 2001) suggested an 'evaluation criteria staircase', in order of descending value of success –probing pocket depth ≤4 mm; no clinical signs of gingival inflammation; no bleeding on probing; no further loss of attachment and no further loss of alveolar bone. Successful treatment could then be categorised as levels on the staircase. A 2002 systematic review (Heitz-Mayfield *et al.*, 2002) on the topic of non-surgical periodontal treatment outcomes used 'reduction in periodontal probing depth, maintenance or improvement in clinical attachment level and reduced bleeding on probing incidence' as their criteria for a successful case. Further evidence based definitions of success are summarised by SDCEP (Scottish Dental Clinical Effectiveness Programme) in which optimal outcomes are plaque scores below 15% (Axelsson *et al.*, 2004, Carnevale *et al.*, 2007), bleeding on probing scores below 10% (Axelsson *et al.*, 2004, Carnevale *et al.*, 2007, Tonetti *et al.*, 1998) and probing depths of less than 4mm (Paulander *et al.*, 2004). Ideally, all three of these targets would be met within the same patient. However, this is not always achievable. Thus, SDCEP have advised that patients showing improvements in oral hygiene, reduced bleeding on probing and a 'considerable' reduction in probing depths from baseline may be categorised as successful. It is therefore evident that defining success in periodontal therapy is not solely related to a single outcome measure – rather a combination of multiple - most commonly periodontal probing depth and bleeding on probing scores. Achieving all parameters of success is a rare event and adopting compromised levels of success has thus become necessary within the current models.

1.7 Systemic Effects of Periodontal Treatment

Non-surgical periodontal treatment consists of thorough supra gingival and subgingival debridement, using a combination of ultrasonic and hand instruments. Combined with patient compliance with bespoke oral hygiene

instruction, this treatment has consistently demonstrated significant improvements in multiple clinical parameters of success including reduced bleeding on probing, probing attachment levels and plaque scores (Badersten *et al.*, 1981). The physical act of non-surgical instrumentation results in unavoidable perturbation to the periodontium. It is assumed that operator induced physical displacement of periodontal microorganisms into local tissues and gingival capillaries allows bacteria to reach the circulation. The incidence of bacteremia following periodontal therapy has been reported to be in the range of 13%-70% (Forner *et al.*, 2006, Kinane *et al.*, 2005, Lofthus *et al.*, 1991). Incidence of bacteremia following ultrasonic scaling, periodontal probing and toothbrushing, was reported as 23%, 16% and 13% respectively (Kinane *et al.*, 2005). Moreover, the DNA of periodontal pathogens has been identified within surgically removed atherosclerotic plaques (Haraszthy *et al.*, 2000, Okuda *et al.*, 2001). This paradigm of systemic spread of oral microorganisms following dental treatment is the basis of an ongoing discussion with regards to requirement for antibiotic prophylaxis during invasive dental treatment, including the non-surgical treatment of periodontal disease. Currently, NICE (National Institute for Health and Care Excellence) guidelines dictate antibiotic prophylaxis is not recommended routinely for people undergoing dental procedures (Centre for Clinical Practice At, 2008). In contrast, the 2007 US (Wilson *et al.*, 2007, Habib *et al.*, 2015) and 2009/2015 European guidelines advise antibiotic prophylaxis regularly for patients with prosthetic heart valves, a positive history of infective endocarditis or congenital heart disease who are undergoing invasive dental procedures.

Potential mechanisms for the systemic dissemination of periodontal bacteria and their products have been proposed. The first relates to the periodontal pocket being separated by only a few cells from the gingival micro-capillaries and it is thought bacteria may have potential to cross this layer and enter circulation via a transcellular mechanism (Takeuchi *et al.*, 2011). Another relates to the ability of pathogens to survive within human immune cells, this remains theoretical however (Carrion *et al.*, 2012, Zeituni *et al.*, 2009). Perhaps the most likely mechanism is that of bacteria entering the blood stream after physical perturbation of the gingivae (Reyes *et al.*, 2013) – through, for example,

mastication, toothbrushing or periodontal instrumentation. This systemic inoculation of bacteria and their by-products has been shown to result in systemic inflammation and bacteraemia. A 2005 study (Kinane *et al.*, 2005) reported an incidence of bacteraemia of 20%, 13%, and 3% for periodontal probing, ultrasonic subgingival instrumentation and toothbrushing respectively. Forner *et al* (Forner *et al.*, 2006) reported an incidence of 70% of bacteraemia following non-surgical periodontal treatment – however patient numbers were limited to 20 subjects. This potentially high incidence of bacteraemia may explain resulting systemic inflammation.

It would therefore appear compelling that bacteria and their by-products are disseminated following non-surgical periodontal therapy. As is apparent, this varies according to intervention, individual patient variation, sampling methods and population studied. The long-term implications for other body systems, existing chronic diseases and of unknown effects of systemic bacterial dissemination are topics of developing contemporary research. To aid our understanding of the host response following bacteriaemia after periodontal treatment specifically, a variety of blood markers have been studied, which will now be discussed.

There are several hallmark serum markers of systemic inflammation, with relevance to the effects of periodontal treatment. The most widely studied of these include C-reactive protein, interleukin 6 (IL-6), interleukin 1 (IL-1) and Tumour Necrosis Factor Alpha (TNF alpha). The latter three each being one of multiple cell signalling proteins known as cytokines. A 2004 study (Ide *et al.*, 2004) monitored TNF alpha and interleukin-6 levels within a non-smoker patient cohort with moderate/severe periodontal disease. Non-surgical periodontal treatment was provided over a 60-minute period, instrumenting all diseased sites within the mouth. Blood samples were taken at various time points following treatment and compared to baseline. Significant increases in both TNF alpha and IL-6 occurred following treatment. Unusually, no significant change in serum CRP was noted – this is in contrast with the consensus finding of an increase in CRP following periodontal therapy. The investigators also demonstrated full clearance of bacterial endotoxin from serum within 15

minutes of periodontal treatment. This is in keeping with a 2006 study by Forner *et al*. (Forner *et al*., 2006) who identified rapid elimination of bacterial endotoxin within 1 hour in the studied population. Again, Forner's group found levels of IL-6 had significantly increased 8 hours following non-surgical treatment. Disease severity was also linked with levels of preoperative IL-6 by this study and others (Mengel *et al*., 2002, Buhlin *et al*., 2003). In relation to CRP levels following treatment, a recent 2018 study (Morozumi *et al*., 2018) identified a 5-fold increase in CRP at the 24-hour mark following non-surgical periodontal treatment. D'Aiuto's study (D'aiuto *et al*., 2004a) of otherwise healthy subjects with severe chronic periodontitis reported a 10-fold increase in CRP following non-surgical treatment.

The majority of recently conducted studies report a predictable increase in combinations of CRP, IL-6, and TNF alpha following non-surgical periodontal treatment (D'aiuto *et al*., 2004a, Graziani *et al*., 2015, Morozumi *et al*., 2018, Radafshar *et al*., 2010, D'aiuto *et al*., 2007, Tonetti *et al*., 2007, Kaptoge *et al*., 2010). The increase and subsequent resolution in CRP and associated factors has been studied longer term following treatment. Two authors (Zhou *et al*., 2013, Marcaccini *et al*., 2009) identified CRP and IL-6 concentrations returning to around baseline levels 3 months after therapy. A 2010 study (Radafshar *et al*., 2010) reported a significant decrease in serum CRP at 4 months, to a level below those at baseline. This study by Radafshar *et al*. investigated CRP and white blood cell counts prior to, and four months following, non-surgical root surface debridement and adjunctive chlorhexidine pocket lavage within a cohort of thirty-five otherwise healthy individuals. In relation to serum CRP reduction, 1.85mg/L was achieved following a mean pre-treatment value of 2.32mg/L, representing a 20% reduction. These findings have identified potential longer-term implications of non-surgical periodontal treatment upon the immune system.

From a clinical perspective, the question arises whether quadrant scaling or full mouth debridement within a short period of time affects the inflammatory state of the patient. Mongardini (Mongardini *et al*., 1999) and Quirynen (Quirynen *et al*., 1999) investigated the effects of full versus partial mouth disinfection in a

mixed aggressive and severe chronic periodontitis patient cohort. 50% of patients who underwent full mouth disinfection reported pyrexia over the following 12 to 24 hours – indicating a possible significant disturbance of systemic inflammatory regulation. Increased body temperatures were also found in studies by Morozumi (Morozumi *et al.*, 2018) in 2018 and Graziani in 2015 (Graziani *et al.*, 2015). Clinical outcomes showed no clinically relevant differences between one stage full mouth debridement – consisting of full mouth instrumentation within 24 hours – and the quadrant by quadrant approach. Graziani *et al* (Graziani *et al.*, 2015) compared full mouth versus quadrant non-surgical periodontal treatment on acute-phase inflammatory marker levels within a randomised controlled trial of ninety subjects. Full mouth treatment resulted in a greater acute phase response 24 hours after treatment. Compared to baseline, this consisted of a 3-fold increase in CRP levels, 2-fold increase in IL-6 levels with a slight increase in TNF alpha levels when compared to quadrant scaling. However, 3 months following treatment, both full mouth and quadrant scaling groups showed no significant difference in systemic inflammatory marker levels and did not identify a net reduction in inflammatory markers, compared to baseline. Despite the relatively small patient numbers within these studies, these findings have potential implications for our daily practice.

Residual periodontal pocketing following non-surgical therapy has been shown to be associated with numerous factors including initial disease severity, higher preoperative bleeding indices and cigarette smoking (Tonetti *et al.*, 1998). One possible treatment approach for residual pocketing is that of periodontal surgery. Graziani *et al.* (Graziani *et al.*, 2010) investigated the effects periodontal surgery may have upon systemic inflammation. Subjects were treated with non-surgical periodontal therapy, followed 180 days later by two episodes of surgical intervention for residual sites with PPDs >5 mm. It was found the greatest increase in post-operative CRP was associated with non-surgical therapy. This result may perhaps be explained by the comparatively localised intervention of surgical therapy, compared to the generalised and potentially more invasive non-surgical treatment stage.

1.8 Systemic Disease and Periodontal Treatment

A recent systematic review and meta-analysis (Teeuw *et al.*, 2014) suggested patients with co-morbid diseases benefitted more from periodontal treatment, compared to healthy controls. In this instance, 'benefitted' refers to reduction in surrogate markers of cardiovascular disease – including serum reductions of CRP, IL-6, TNF alpha, total cholesterol and HDL-C. These diseases all share the commonality of chronic inflammation and often share common risk factors such as obesity and smoking habit. The first of these conditions is that of cardiovascular disease. Population studies have identified acute inflammation as a significant risk factor for vascular events such as myocardial infarction or stroke (Smeeth *et al.*, 2004). Patients with cardiovascular disease have a pre-existing vascular dysfunctional state. Further disturbance due to periodontitis and its treatment has potentially significant clinical implications. Persistent low-grade inflammation is thought to be relevant to vascular diseases and vascular risk (Wu *et al.*, 2000); however, the specific mechanisms are currently not well understood (Kaptoge *et al.*, 2010). The general population tend to have relatively stable levels of inflammatory markers, aside from small spikes related to low level infections or trauma (Pepys and Hirschfield, 2003). In healthy adults, the baseline concentration of CRP has been reported at values between <1mg/l and 10mg/L (Pepys and Hirschfield, 2003, Li *et al.*, 2010, Patil and Desai, 2013). This value may increase by up to 10,000 fold during periods of acute infection or significant trauma (Pepys and Hirschfield, 2003) – for example, acute periapical abscess and road traffic accident respectively. Chronic periodontitis has been shown to result in a raised baseline level of CRP – within the region of 2-7mg/l (Goyal *et al.*, 2014, Slade *et al.*, 2003, Thakare and Thakare Ks, 2010). This range is explained by variations in environmental factors within studied populations. The CANTOS study (Ridker *et al.*, 2017) of 2017 studied 10,061 patients with previous myocardial infarction and a CRP level of at least 2mg. Patients received drug interventions targeting an inflammatory mediator pathway. Clinically relevant hard outcomes of nonfatal myocardial infarction, nonfatal stroke or cardiovascular death were measured. The authors assumed each drug intervention would result in a 20% lower rate of event outcome than placebo. With this assumption, in order to gain a 90% power, 1400

primary end points were required from the 10,061 study participants. The most effective dose demonstrated a 70% reduction in CRP levels. effects. Baseline median CRP level across all subjects was 4.15 mg/L which reduced to 1.80mg/L following drug intervention at the three-month mark. This reduction was largely maintained throughout the study's 48-month duration, if all drug dose effects are combined. The authors concluded reduction in even low-grade inflammation has beneficial effects on hard clinical outcomes of cardiovascular disease. As in otherwise healthy periodontitis patient populations, studies in patients with CVD have shown a modest improvement in acute phase inflammatory markers as a result of periodontal treatment (Koppolu *et al.*, 2013) with associated short term spike in inflammatory markers in patients with cardiovascular disease. An observational study by Ridker *et al.* (Ridker *et al.*, 2000), studying 14,916 healthy men and controlling for risk factors relevant to cardiovascular disease, observed increased levels of IL-6 at baseline resulted in greater risk of developing myocardial infarction later in life. A level of 1.81 pg/ml of circulating serum IL-6 vs a level of 1.46 pg/ml was shown to result in a significant increase in myocardial infarction incidence in this study. To put this figure into perspective, serum IL-6 has been demonstrated to reside around 5-16 pg/ml for patients suffering from generalised chronic periodontitis (Blach *et al.*, 2009, Monea *et al.*, 2014, Sezer *et al.*, 2012). A 2013 joint statement from the European Federation of Periodontology and the American Academy of Periodontology (Tonetti and Van Dyke, 2013) concluded consistent and strong epidemiologic evidence exists that periodontitis imparts increased risk for future cardiovascular disease development. In partial agreement, the American Heart Foundation released a scientific statement in April 2012 stating observational studies to date support an association between periodontitis and cardiovascular disease. However, 'they do not support a causative relationship'. Further well-structured interventional trials are required to establish a direct cause-effect relationship, in particular in relation to the beneficial effects of treatment.

Recent interventional studies have analysed endothelial function following periodontal therapy, as a method of predicting possible risk of vascular events. The endothelium is the cellular lining of blood and lymphatic vessels. Healthy endothelium is responsible for regulating vascular resistance and the release of

various mediators involved in regulation of oxidative stress – thus maintaining a healthy cardiovascular system. Tonetti *et al* (Tonetti *et al.*, 2007) assessed endothelial function by means of the diameter of branchial artery flow, comparing full mouth and quadrant debridement protocols. Twenty-four hours after periodontal therapy, levels of CRP and IL-6 were significantly increased. Full mouth periodontal treatment was identified as causing acute, short term systemic inflammation and endothelial dysfunction. However, 6 months following therapy, endothelial function was improved beyond baseline levels – resulting in a cardiovascular benefit to the patient.

Improvements in endothelial function following periodontal treatment were consistently reported in a 2014 systematic review and meta-analysis by Teeuw (Teeuw *et al.*, 2014). Benefits upon CRP, TNF alpha, fibrinogen, total cholesterol and HDL-C were identified. Humphrey (Humphrey *et al.*, 2008) reported an increase in relative risk for developing cardiovascular disease in subjects with untreated periodontitis in the range of 1.24 to 1.34. With regards to the risk of suffering a stroke, another meta-analysis in 2003 (Janket *et al.*, 2003) reported a relative risk of 1.85 compared to subjects without periodontal disease. Teeuw's systematic review reported endothelial and cardiovascular benefits from periodontal therapy are sustained over at least 6 months with the overall effect on endothelial function from periodontal disease being positive.

A review on the subject of the impact of periodontal treatment on systemic health by D'Aiuto (D'aiuto *et al.*, 2013) warned that the proliferation of a surrogate outcome such as endothelial dysfunction as a predictor of future cardiovascular risk and outcomes should be used with caution. The authors describe it as a 'research measure that is greatly confounded by multiple methodological and environmental factors' and as such may prove unreliable. They suggest 'alternative, more proven measures of sub-clinical atherosclerosis such as c-IMT may show a more consistent association with future risk of cardiovascular disease'. The absolute marker of cardiovascular outcome would be a cardiovascular event such as a myocardial infarction however this has evident ethical implications for study design. The American Heart Association in 2012 (Lockhart *et al.*, 2012) issued a statement concluding that no causative

relationship between periodontal disease and atherosclerotic vascular disease currently exists. As is evidenced in the literature, periodontal intervention has potential to result in overall reduction in systemic inflammation and improvement in endothelial function in short term studies, however, evidence of prevention of cardiovascular events is notably lacking.

Poor diabetic control may lead to diabetic complications such as neuropathy, retinopathy, ketoacidosis and high blood pressure among others. A 2013 review (Engebretson and Kocher, 2013) established consistent albeit modest effects upon HbA1c levels as a result of periodontal therapy in subjects with Type 2 diabetes. Some individual studies record significant improvements in HbA1c levels following periodontal therapy. A Cochrane Collaboration review (Simpson *et al.*, 2015) found a mean percentage reduction in HbA1c of 0.29% 4 months after treatment. The review concluded that insufficient evidence was available to comment after a four-month period, with no single periodontal treatment modality emerging as more beneficial to diabetic control. More recently, D'Aiuto's review in 2017 (D'aiuto *et al.*, 2017) concluded there is no evidence that the beneficial effect of periodontal treatment upon diabetic control is sustained over the long-term nor reduces the prevalence of long term diabetic complications. To evidence available to date, suggests periodontal treatment has favourable effects upon HbA1c and by extension diabetic control. However, more well designed, long term interventional trials are required to substantiate this.

1.9 Summary

Periodontitis is evidently a multifaceted, complex disease process with emergent links to systemic health and disease. Non-surgical treatment for periodontitis is effective by various instrumentation approaches and has a wealth of supporting evidence, as presented in this chapter. Instrumentation approach, thus far, has been largely down to clinician preference. The economic burden of periodontal disease is only increasing, and time and cost efficiency of treatment may prove to be an important factor for future service development in the United Kingdom – this warrants exploration. Further detailing of the clinical effectiveness and the patient centred nature of periodontal instrumentation techniques would be highly valuable. The comparative effects of instrumentation techniques upon markers of systemic inflammation is another topic of significant interest to develop the contemporary evidence base in modern, holistic periodontal treatments. Studies carried out within the field of systemic inflammation following periodontal therapy have, thus far, been done solely on the basis of a combination approach to treatment. A need therefore exists for comparative research investigating inflammatory outcomes of non-surgical instrumentation techniques for the treatment of periodontitis.

This study aims to explore clinical and systemic inflammatory outcomes in relation to three methods of non-surgical instrumentation for the treatment of periodontitis – ultrasonic instrumentation, hand instrumentation and a combination approach ('treatment as normal'). Multiple research questions were developed – each aimed at addressing a specific facet of interest.

1.10 Objectives and Research Questions

The objective of the current work is to compare three techniques of non-surgical treatment for the treatment periodontal disease – exclusively ultrasonic instrumentation, exclusively hand instrumentation and a combination approach. This study is a post-hoc analysis of two existing studies. This analysis was

designed to evaluate periodontal treatment (comparing baseline and ninety days following completion of treatment), using three different instrumentation methods with regards to clinical outcome (measured via PISA, PPD, % Pockets ≥5mm, BOP and plaque scores), objective 'success' of treatment (measured against published criteria), time taken for treatment (measured in minutes), systemic inflammatory outcomes (measured via CRP level), financial aspects and patient reported outcomes. The research questions were as follows:

1. Clinical parameters of periodontal disease status
    a. What are the effects on clinical periodontal outcomes, measured 90 days following treatment (comparing baseline with day 90), for each treatment group?
    b. Is there a difference in clinical outcome between treatment groups?
    c. How is clinical outcome affected by particular key confounders?
    d. Was treatment for study patients successful in the context of published criteria of a successful outcome of periodontal treatment?
2. Time taken for treatment
    a. Is there a difference in time taken for treatment comparing treatment with hand instruments, to ultrasonic instruments, to combination instruments?
3. Systemic inflammation
    a. Does CRP immediately increase following periodontal treatment?
    b. Is there a difference between treatment groups with respect to day 90 post-treatment levels of CRP?
4. Financial Implications
    a. What are the costs of providing periodontal treatment within a secondary care UK dental hospital setting - comparing single modality treatment provided using a full mouth debridement approach (assuming 2 visits in 24 hours) to combination treatment provided using a quadrant by quadrant approach?
5. Patient reported outcomes
    a. What were patient experiences of receiving periodontal treatment?

Chapter 2: Methods

The work presented in this thesis combines data sets from two separate studies. Both studies were carried out within Glasgow Dental Hospital. One study, 'Study 1,' was a randomised controlled trial comparing use of hand with ultrasonic instruments on changes in systemic inflammation following non-surgical periodontal treatment. The other, 'Study 2,' was a cohort study in which patients were treated with a 'standard of care' approach that used both hand and ultrasonic instruments and also investigated systemic inflammation following periodontal treatment. The research questions addressed in this work sought to compare different aspects of periodontal treatment provided across a total of three treatment groups. Each of the two studies is described individually below, and the approach to comparing the three treatment groups described subsequently.

2.1 Randomised Controlled Trial (RCT) – 'Study 1'

This Randomised Controlled Trial, "The **I**mmune **R**esponse **A**fter **P**eriodontal **T**reatment" (IRAPT) was designed to evaluate a primary outcome of systemic inflammatory changes following either hand instrumentation or ultrasonic instrumentation for the non-surgical treatment of periodontal disease. This trial was registered through ClinicalTrials.gov, ID – NCT03501316, prior to recruitment. The Research Ethics Committee reference was 18/NI/0059 and ethics was approved on 13th March 2018 by the Office for Research Ethics Committees Northern Ireland (ORECNI). The study was active between February 2018 and June 2019.

The PICO question that IRAPT aimed to answer: 'For patients with periodontitis (problem/population), following non-surgical periodontal treatment (intervention), is there a difference in changes in systemic inflammatory markers (outcome) comparing treatment provided by exclusively hand instruments or exclusively ultrasonic instruments (comparison)?'

'IRAPT' was a single centre randomised controlled trial with two intervention arms, with patients returning at day 1, day 7 and day 90 post treatment, following separate baseline and treatment visits. Patients were referred by their

General Dental Practitioner (GDP) to Unit of Periodontics at Glasgow Dental Hospital for specialist management of periodontal disease. Patients were approached during new patient assessment clinics in the Unit of Periodontics. All participants gave informed, written consent.

2.1.1 RCT - Inclusion and Exclusion Criteria

The inclusion criteria for the RCT were:

- Male or female patients aged 18 years to 70 years inclusive
- Probing depths ≥ 5 mm on 2 or more teeth at non-adjacent sites with cumulative probing depths of ≥ 40 mm. Cumulative probing depth was calculated by examining six sites on each tooth. The deepest site on each tooth was recorded and if the value was greater than 4 mm, this contributed to the cumulative total, with each tooth being only counted once towards the total to ensure extent of disease. The use of cumulative probing pocket depth ensured a minimum level of periodontal disease (≥ 2 sites with probing depths with ≥ 5 mm) (Page and Eke, 2007, Tonetti and Claffey, 2005), and has recently been adopted as a means of including patients with a disease burden that is potentially relevant to systemic inflammation (Serban *et al.*, 2019, Lopez-Oliva Santa Cruz, 2018).

Exclusion criteria included:

- known or suspected high risk for tuberculosis,
- hepatitis B or HIV infections;
- required interpreter/non-English language written material to understand and provide written, informed consent, or any other reason for being unable to provide written, informed consent;
- history of bleeding diathesis;
- pregnant or lactating females;
- self-reported diagnosis of any systemic illnesses including cardiovascular, renal, and liver diseases, and/or regular use of medication to control systemic illness;

- any pharmacological treatment within 1 month before the beginning of the study, including routine use of any over the counter medications,
- specialist periodontal treatment in the previous 6 months.

2.1.2 RCT - Study Procedures

Following referral to Glasgow Dental Hospital by their GDP, eligible patients were initially informed of the existence of the study and approached by the consultant or his/her representative who was treating the patient (specialty dentist, dental core trainee, hygienist or specialty trainee in Restorative Dentistry). This initial contact was to provide the patient with the Participant Information Leaflet (PIL – Appendix I) and establish whether they would consider taking part. At the subsequent visit (Screening visit), the researcher asked whether the patient would like to take part and obtained written consent (Appendix II). At each stage, it was made clear to the patient that participation is voluntary and they could leave the study at any time without their care being affected.

At the baseline visit, patients were provided with detailed oral hygiene instruction, dental health education and a full-mouth supragingival scale (using a Cavitron Powerline FSI-10 30K FITGRIP Insert), irrespective of treatment group. Medical history was confirmed to be clear and smoking status was recorded as ‘current, former or never’, with detail on amount smoked and time period as appropriate. All interventions and clinical data collection were carried out by an experienced dental hygienist (DM) and/or specialist trainee in restorative dentistry (MP). SC was the named principle investigator. For calibration, both examiners completed pocket charts on the first twelve patients entering the study. Charts were assessed for agreement and a kappa score was calculated (0.66). Following collection of blood samples at day 1 post treatment, all patients were provided with an electric toothbrush (Oral-B Pro 2000) to standardise self-performed plaque control prior to day 90 follow-up.

2.1.3 RCT - Clinical Outcomes

At baseline and day 90, clinical parameters (full-mouth plaque, bleeding scores and detailed 6-point periodontal pocket charting) were assessed using a PCP-12 periodontal probe at six sites per tooth, excluding third molars (unless other molar units missing), with measurements rounded to the nearest millimetre. Following collection of clinical data, the Periodontal Inflamed Surface Area (PISA) was calculated (Nesse *et al.*, 2008).

Regarding systemic inflammation data: CRP was measured at all timepoints (baseline, day 1, day 7 and day 90). Levels of serum CRP were determined by high sensitivity immunoturbidometry using the Cobas C311 analyser (Cobas, Roche Diagnostic, Mannheim, Germany). CRP was detected in all samples. All laboratory assays were conducted following study completion by laboratory staff masked to treatment groups. Analysis of serum CRP was performed at the British Heart Foundation Glasgow Cardiovascular Research Centre. Intra- and inter-assay coefficients of variations were <5%. A single patient in the Hand Instrumentation group was excluded from analysis following completion of interventions due to an abnormally high baseline CRP level and thus was deemed as not adhering to inclusion/exclusion criteria.

2.1.4 RCT - Randomisation

Patients were randomised to one of two treatments (HI or UI) (Figure 2-1, Figure 2-2). Randomization was performed using a computerised random number generator (using permuted blocks of 4 and 6) by the study statistician. Patients were stratified according to smoking status prior to randomization. Concealment of allocation was achieved using an opaque sequentially numbered envelope containing the allocated intervention arm for the patient. This was opened immediately before treatment was commenced.

Patients and clinicians were unaware of intervention until the intervention visit. Clinicians were blinded to treatment groups during post-treatment follow up visits (day 1, day 7, day 90). Statistical and laboratory personnel remained

blinded to specific patient group allocation throughout the entire process via patient codes. The key linking codes to patients was available only to the chief investigator - and was kept on a separate system. Intervention codes were only available once all analyses took place.

Ultrasonic Instruments (left to right)-
Cavitron® Slimline® 10S 30K,
Cavitron® Slimline® 1000 30K,
Cavitron® Slimline® 10L 30K,
Cavitron® Slimline® 10R 30K,
Cavitron® Thinsert® 30K,
Cavitron® Powerline® 1000 30K; Dentsply Sirona

Hand Instruments (left to right)-
Gracey 1/2,
Gracey 7/8,
Gracey 11/12,
Gracey 13/14,
Columbia 4L-4R
Hoe Scaler-lateral,
Hoe Scaler-posterior; LM Dental

Figure 2-1: Instruments used in each Randomised Controlled Trial Treatment Group

Periodontal instruments used within the two treatment groups of the randomised controlled trial: exclusively ultrasonic instruments (upper panel) or exclusively hand instruments (lower panel).

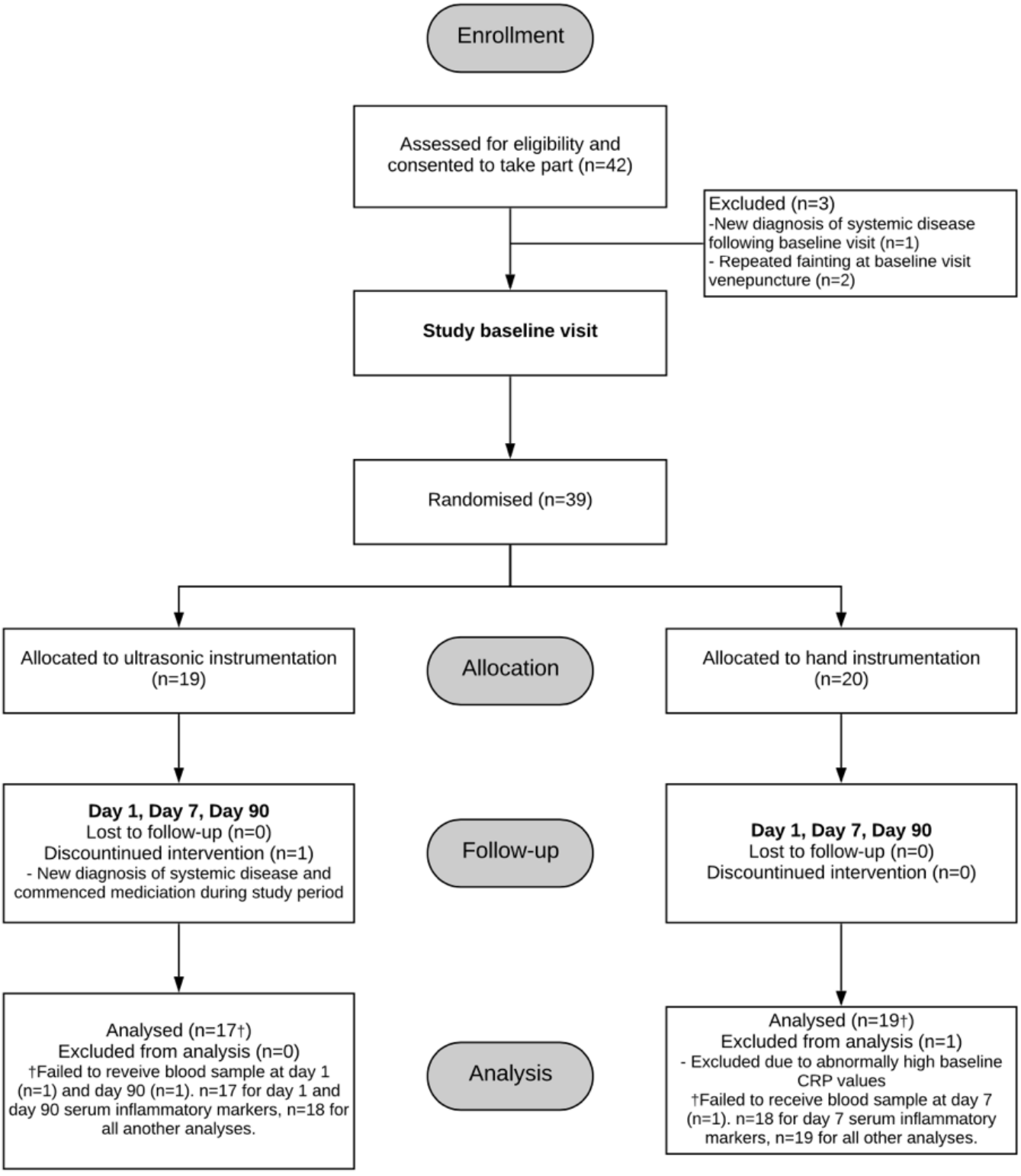

Figure 2-2: CONSORT flow diagram for randomised controlled trial.

Blood samples were not obtained from one patient at day 1 (UI group), one patient at day 7 (HI group) and one patient at day 90 (UI group). Therefore, for analysis of serum inflammatory markers; at day 1 (UI; n=17, HI; n=19), day 7 (UI; n=18, HI; n=18) and day 90 (UI; n=17, HI; n=19). For analysis of clinical parameters and treatment time (UI; n=18, HI; n=19).

Full-mouth debridement was carried out within a 24-hour period. All but one patient completed treatment within the same day; a single patient completed debridement on consecutive days, within 24 hours, due to patient availability. Debridement was completed using Gracey and Universal curettes (Gracey 1/2, Gracey 7/8, Gracey 9/10, Gracey 11/12, Gracey 13/14, Columbia 4L-4R) and hoes (Hoe Scaler-lateral, Hoe Scaler-posterior, LM Dental) for the hand instrumentation (HI) group; or Cavitron Ultrasonic inserts (Cavitron® Thinsert® 30K, Cavitron® Slimline® 10S 30K, Cavitron® Slimline® 10L 30K, Cavitron® Slimline® 10R 30K, Cavitron® Slimline® 1000 30K, Cavitron® Powerline® 1000 30K; Dentsply Sirona) for the ultrasonic instrumentation (UI) group (Figure 2-1).

Treatment was provided with the aid of local anaesthetic and timed by digital stopwatch from the point of first contact between instrument and tooth surface. Debridement was carried out until no supra or subgingival plaque or calculus deposits were detectable by visual examination with magnification or by tactile examination. Patients were recalled following periodontal treatment at day 1, day 7, and day 90. Samples were collected as per baseline visit (serum, whole blood, saliva, subgingival plaque, GCF) at each timepoint, with clinical parameters measured at day 90 only. Following day 90 review, any further treatment need was evaluated by a Specialist in Periodontology.

2.1.5 RCT - Sample size calculation

The primary outcome for the randomised controlled trial was:

- Serum CRP levels at day 1 post-treatment

Secondary outcomes were:

- CRP at day 7 and day 90
- Other systemic inflammatory markers (IL-6, TNF alpha) at day 1, day 7 and day 90
- Subgingival plaque microbiome analysis at day 1, day 7 and day 90
- Clinical parameters at day 90 (PISA, PPD, % Pockets ≥5mm, BOP, CAL)
- Treatment time
- Patient reported outcomes

The sample size calculation was based on data from a previous study that measured changes in CRP following periodontal treatment (Graziani *et al.*, 2015). From this study, a difference of 3.5 mg/l (SD=3 mg/L) in serum CRP was detected between the two groups receiving different schedules of periodontal treatment (quadrant vs full-mouth debridement), 24 hours after completion of treatment. This magnitude of difference has been deemed clinically relevant in recent guidelines (Sanz *et al.*, 2020), therefore this was considered a reasonable estimate of the minimum clinically relevant difference. At 80% power and a 5% significance level, a sample size of n=34 (17 in each group) was required to detect a minimum difference of at least 3mg/l (=1 SD) between CRP levels at primary endpoint (day 1) between the two groups (HI vs UI). To account for potential drop-out of 20%, 42 eligible patients were recruited.

2.1.6 RCT – Summary of Data Yield

This trial provided clinical data relating to outcomes of treatment with exclusively hand instruments or exclusively ultrasonic instrumentation, using a full mouth approach within 24 hours. All patients included for final analysis in this trial (Figure 2-2) were included in the current post hoc analysis study.

2.2 Cohort Study - 'Study 2'

The comparator data set (combination instrumentation) was gathered from a cohort study ('Immune Response in Periodontal Disease') carried out within the same centre as the RCT. The study was active between August 2017 and September 2018. The cohort study was designed as an exploratory study to evaluate changes in serum antibodies and other inflammatory mediators following periodontal treatment. Treatment in this study was delivered using a combination of hand and ultrasonic instrumentation using a quadrant approach by a single experienced dental hygienist (DM). Data analysis for the purposes of the current study was carried out by MP. SC was the named principle investigator. A further extension of this study involved retention of surplus tissue during surgical periodontal treatment – this aspect is not discussed herein as it is

not relevant to the current study. The research ethics committee number (REC reference) for this study was 14/LO/2064. The Integrated Research Application System ID was 149159.

2.2.1 Cohort Study – Inclusion and Exclusion Criteria

Inclusion criteria were as follows:

- Written informed consent
- Male or female ≥18 years of age
- Periodontal treatment required at Glasgow Dental Hospital

Exclusion criteria were:

- Known or suspected high risk for tuberculosis, hepatitis B or HIV infections
- Require interpreter/non English language written material to understand and provide, or any other reason for being unable to provide written, informed consent
- History of bleeding diathesis

2.2.2 Cohort Study – Study Procedures and Sample Collection

2.2.2.1 Visit 1: New Patient Assessment

Patients were referred then appointed on a new patient consultant clinic at which a clinical history and clinical examination were completed by a consultant or his/her staff. A treatment plan was then agreed with the patient. If this treatment plan included periodontal treatment at Glasgow Dental Hospital then the patient was provided with written (Patient Information Leaflet – Appendix III) and verbal information about the study. If the patient indicated they would consider participation in the study, they were appointed jointly to the Clinical Research Facility and the study hygienist (visit 2) following recorded informed consent (Appendix IV).

2.2.2.2 Visit 2: Initial treatment visit

This visit was for initial periodontal treatment and collection of baseline clinical information including smoking status ('current', 'former', 'never') Periodontal Probing depths (PPD), Bleeding on Probing % (BOP) and plaque %. This visit included detailed oral hygiene instruction and a superficial ultrasonic scaling of the teeth (Cavitron® Powerline® 1000 30K; Dentsply Sirona). Consent for sample collection was confirmed and samples were collected by the research nurse (whole blood) and study hygienist (in the case of subgingival plaque, saliva and gingival crevicular fluid).

2.2.2.3 Subsequent treatment visits

The number of visits varied, subject to extent of treatment required and patient preference for treatment scheduling. At the final treatment visit, the study hygienist verbally enquired whether the patient was happy to continue participation in the study. If yes - then the review visit (at Day 90 following treatment) was scheduled within the Clinical Research Facility for sample collection.

2.2.2.4 Day 90 review visit:

Patients were appointed to the Clinical Research Facility for review, 90 days (±14 days) following completion of periodontal treatment, to assess requirement for further treatment with a consultant or training grade staff under consultant supervision. Data and samples were collected, as per visit 2 – periodontal probing depths, plaque %, BOP % and whole blood with the addition of plaque, saliva and gingival crevicular fluid. Techniques of clinical sample collection are identical to those described in Section 2.1.3.

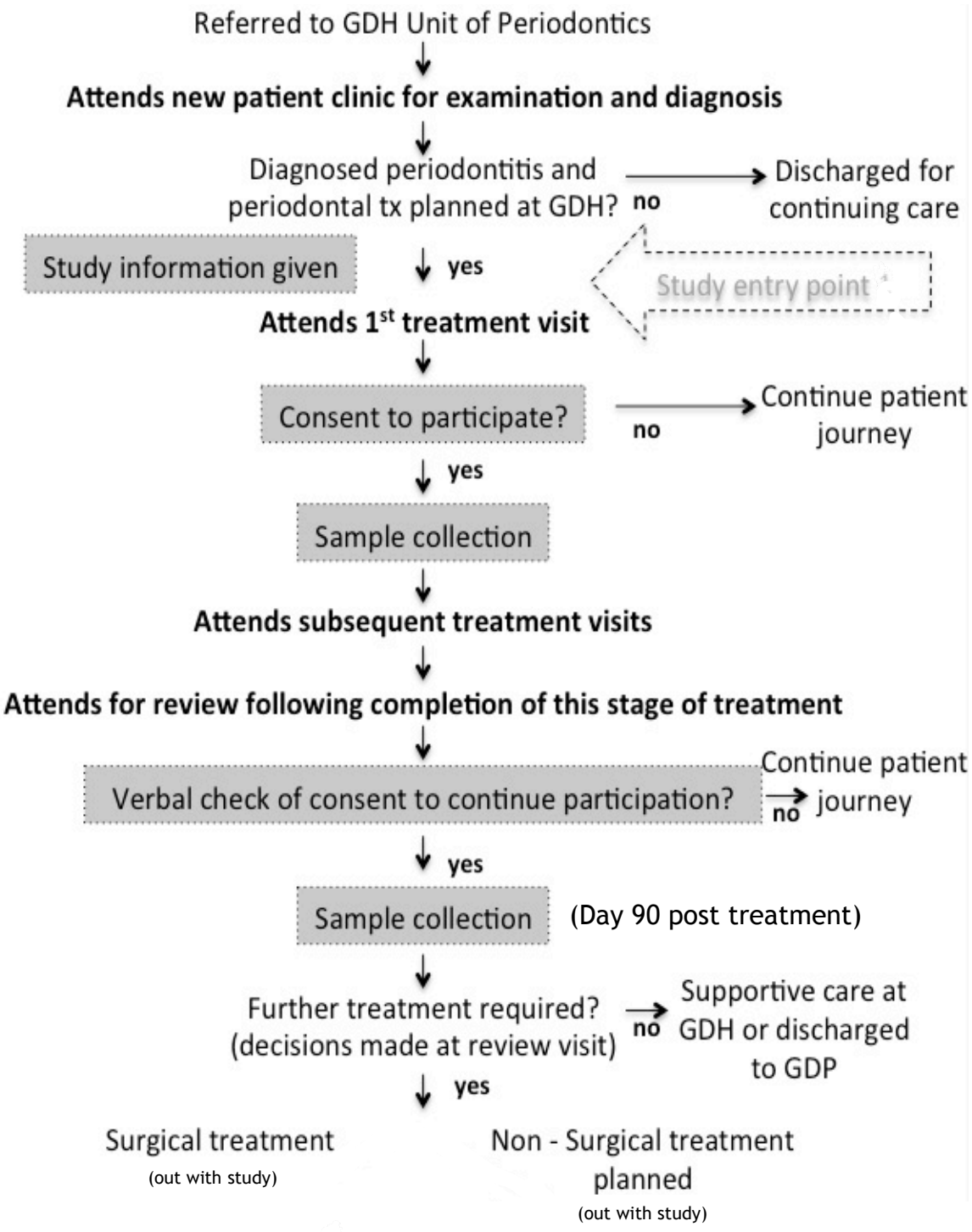

Figure 2-3: Patient flow diagram for cohort study.

Patients attended for periodontal treatment using a combination approach and provided over as many appointments as necessary – as judged by the treating research hygienist.

2.2.2.5 Cohort Study – Summary of Data Yield

This study provided clinical and systemic inflammation data pertaining to periodontal instrumentation using a combination of hand instruments and ultrasonic instruments.

2.3 Current Study Protocols

2.3.1 Sample Size

The sample size of the current study was dictated initially by the number of patients completing all interventions in each of the RCT's two treatment groups (n=19; n=18 respectively) – "Study 1". This information was used to select a similar number of patients (n=18) from the cohort study ("Study 2") to serve as a third comparator group. The process of patient selection is described subsequently. This sample size was deemed sufficient to allow the assessment of trends for exploratory analysis.

2.3.2 Patient Selection Process

All patients in the RCT were included for analysis. Patients were selected from the cohort study by matching of patients to the inclusion/exclusion criteria as per the RCT to minimise heterogeneity in characteristics of patients. Therefore, all patients analysed in this study fulfilled the following inclusion/exclusion criteria:

2.3.2.1 Inclusion criteria

- Written informed consent
- Male or female 18 years to 70 years inclusive
- Periodontal treatment required at Glasgow Dental Hospital
- Probing pocket depths >5mm on 2 or more teeth at non-adjacent sites with cumulative probing pocket depths of greater than or equal to 40 mm (Cumulative probing depth is calculated by evaluating all sites on each tooth. The deepest site on each tooth is recorded and if this value is greater than 4 mm this is 'counted' and the sum of all the teeth assessed in this way calculated.)

2.3.2.2 Exclusion criteria

- Known or suspected high risk for tuberculosis, hepatitis B or HIV infections

- Require interpreter/non English language written material to understand and provide, or any other reason for being unable to provide written, informed consent
- History of bleeding diathesis
- Pregnant or lactacting females.
- Reported diagnosis of any systemic illnesses including cardiovascular, renal, and liver diseases, and/or regular use of medication to control systemic illness.
- Any pharmacological treatment within 1 month before the beginning of the study, including routine use of any over the counter medications.
- Specialist Periodontal treatment in the previous 6 months.

2.3.3 Study Outcome Data

2.3.3.1 Clinical Outcome Data

Data on periodontal clinical outcomes were collected within the RCT and cohort studies. Periodontal outcomes were assessed via PISA, PPD, % Pockets ≥5mm, BOP and plaque scores. Systemic inflammatory outcomes were assessed via serum CRP level.

Details of clinical outcome data collection techniques are presented in Section 2.1.3 and a schedule of collection is presented in Figure 2-4.

2.3.3.2 Financial Outcome Data

Financial costs of periodontal treatment were estimated through discussion with onsite centralised medical device sterilisation services and NHS procurement staff. Salary data of individuals involved in periodontal care (clinicians, nursing and CCSD staff) was not included in the current data set as the aim was not to estimate the total treatment cost. The data focused on differences in ‘fixed’ costs (i.e. instruments) and time taken. The impact of salary costs varies according to staff type. Understanding time taken provides the multiplier for the appropriate staff cost.

Data were derived from protocols within the current studies thus all available inserts (Cavitron® Thinsert® 30K, Cavitron® Slimline® 10S 30K, Cavitron® Slimline® 10L 30K, Cavitron® Slimline® 10R 30K, Cavitron® Slimline® 1000 30K, Cavitron® Powerline® 1000 30K; Dentsply Sirona) for ultrasonic instrumentation and the full hand instrument scaling kit (Gracey and Universal curettes (Gracey 1/2, Gracey 7/8, Gracey 9/10, Gracey 11/12, Gracey 13/14, Columbia 4L-4R) and hoes (Hoe Scaler-lateral, Hoe Scaler-posterior, LM Dental)) were considered.

2.3.3.3 Patient Reported Outcomes

Patients taking part in the RCT were presented with two open written questions at each follow up (Day 1, Day 7, Day 90). Questions were designed following collaboration with a behavioural psychologist and constructed to be open ended and minimise time commitment from trial patients. It was felt patients should not be burdened with an extensive questionnaire – in the context of other time commitments arising from the trial (e.g. blood sampling and follow up visits). These were as follows:

- 'Thinking about the treatment in your own words, can you describe the experience of treatment?'

And

- 'Is there anything that would have made it a better experience?'

These questions were posed to patients at Day 1, Day 7 and Day 90 after treatment and were selected to allow patients freedom to provide descriptions relating to treatment received. Following completion of questions, answers were collated, and themes analysed.

2.3.4 Ethical Approval

Ethical approval was granted by application to the Greater Glasgow and Clyde Health Board and Office for Research Ethics Committees Northern Ireland (ORECNI) for both studies which served to provide data for the current analysis. This study, being a post hoc analysis, required no separate ethical approval.

2.3.5 Patient Flow

The patient flow through the RCT and cohort studies and data collection points are shown in Figure 2-4. The two studies are described in detail in Section 2.1 and Section 2.2 of this chapter.

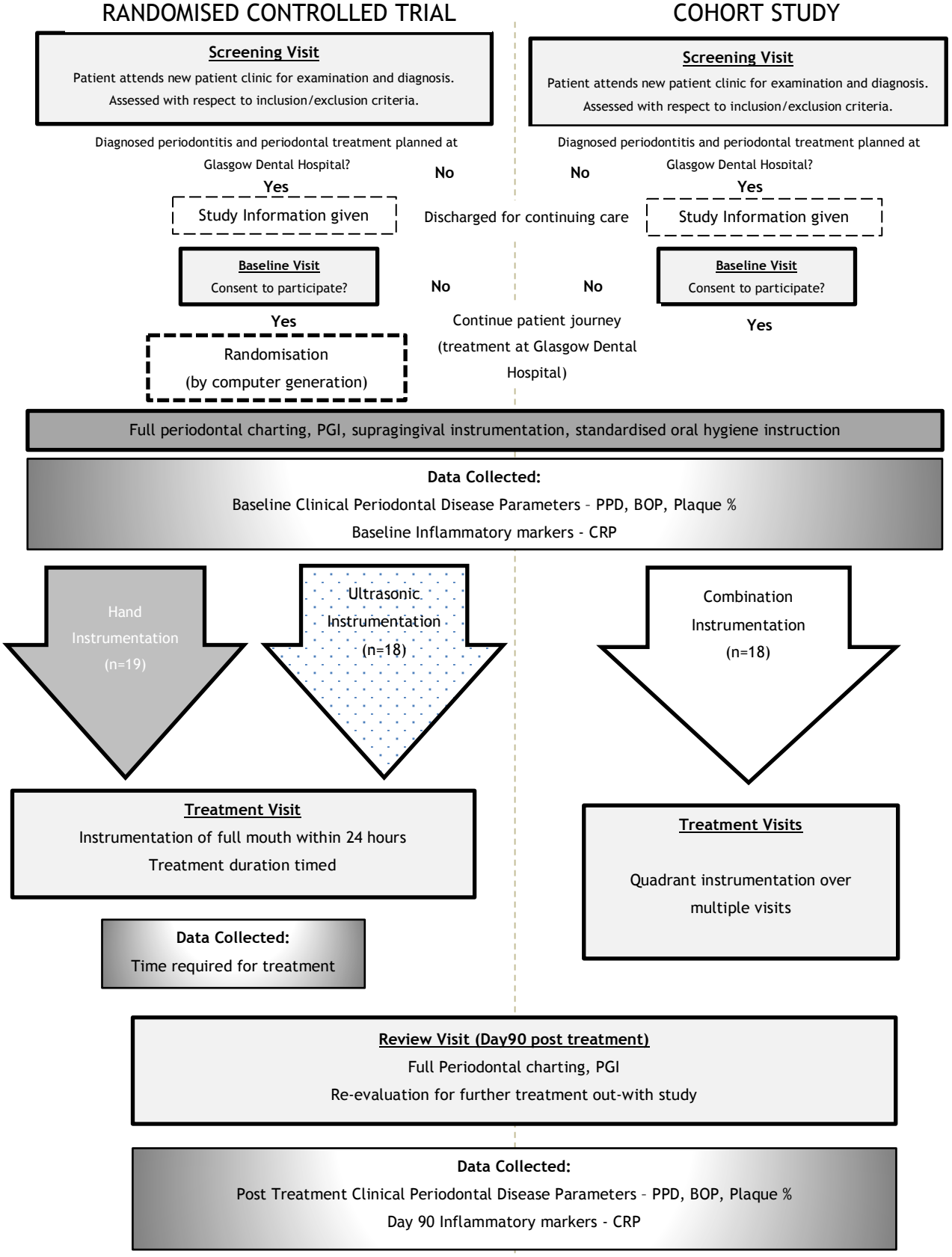

Figure 2-4 – Patient flow through respective studies.

Please note trials did not occur in parallel. Patients were recruited from new patient periodontology clinics within Glasgow Dental Hospital. Following eligibility assessment and consent processes, patients within the randomised controlled trial underwent randomisation. A baseline visit was carried out which was consistent across both studies. Baseline clinical and systemic inflammation data collection occurred at this stage. Interventions were then provided as per separate study. Patients were reviewed 90 days following intervention completion, consistent across both studies, with post treatment clinical periodontal parameters and systemic inflammation data collection.

2.3.6 Statistical Analysis

All data were analysed using SPSS Software Version 25 (SPSS Inc. Chicago, IL, USA). All data were cleaned and checked for range errors/logical errors/ inconsistencies.

Regarding Data Management, a file naming convention was adopted using unique, anonymised subject identifiers relevant to the data set. Data were transcribed from a paper form in the CRF (Clinical Research Facility) to a secure password protected directory on the university "One Drive" by MP and WJ. All personal identifiers were removed and replaced with an anonymised code. The link between the personal identifiers and anonymised code was held on a separate system and only accessible by SC (the PI). All files were categorised using intuitive filenames that denoted the date created, researcher inputting data and a relevant descriptor. Each file had an included ReadMe file which informed the user of what the naming convention is, when the data was created, how the data was created and what software is needed to open and interpret the data.

Raw and analysed data were kept separate and identifiable through folder labels. Raw data was not edited.

Data was stored through the University of Glasgow approved OneDrive for Business, only accessible to the researcher (MP).

Access to data linking patient name to study code was restricted only to the chief investigator of the RCT and cohort studies (Professor Shauna Culshaw).

Variables were described and summarised using means (standard deviations) or medians (Q1, Q3) as appropriate.

All patients that completed interventions in the RCT were included in the current study apart from a single patient in the hand instrumentation group who was excluded as an outlier due to high baseline CRP.

Data were examined for normal distribution visually using histograms. Non-parametrically distributed data were transformed by natural logarithmic transformation where appropriate.

Baseline data were largely normally distributed (BMI, number of teeth, PPD, Full mouth BOP, Full mouth Plaque, CAL, Pockets ≥5mm); however, multiple variables showed non-normal distribution at Day 90 follow up (Pockets ≥5mm, BOP, Plaque). Univariate general linear models were used to test "between group" differences in clinical variables adjusting for baseline clinical outcome and key confounders (smoking status, treatment time, age, gender, number of teeth) where appropriate. Non-symmetric outcome (dependent) variables were Ln-transformed. Intra group comparisons were carried out using Wilcoxon signed rank test due to Day 90 data commonly being non-normally distributed. Parameter estimates (unadjusted and adjusted), 95% confidence intervals and exact p-values were all presented.

Independent sample t-tests were used to test differences in treatment time between groups. Pearson's correlation coefficients were used to examine the association between treatment time and disease severity (measured by PISA and % of pockets ≥5mm).

Patient reported outcome qualitative data were analysed by descriptive analysis only, with the support of a behavioural psychologist, and emergent themes were identified and described.

2.3.7 Modelling Strategy

General Linear Models were used to assess the effect of different "treatment" groups on clinical outcomes. In the first instance univariable models were produced (Model 1), then models adjusting for the baseline clinical measure were produced (Model 2). Model 3 considered baseline measures for the clinical outcome and smoking status, Model 4 adjusted for baseline measures of clinical outcome, smoking status and treatment time and a final model, Model 5 was adjusted for baseline measures of clinical outcome, smoking status, treatment

time, age, gender and number of teeth. Changes in parameter estimates were used to quantify effects of confounders on clinical outcomes observed.

2.3.8 Sponsorship and Funding

This study received no direct sponsorship or funding however fees associated with undertaking an MSc were partially funded by NHS Greater Glasgow and Clyde staff bursary programme. The Randomised Controlled Trial was funded jointly as a University of Glasgow Industrial PhD Partnership with Dentsply Sirona.

The funding below contributed to support of the cohort study, which was also supported by NHS Greater Glasgow and Clyde:

- *T cells and Teeth – what do oral mucosal T cells do in health and disease* The Sir Jules Thorn PhD Studentship. £84,000 *September 2013-September 2016*
- *Senior Clinical Research Fellowship.* Scottish Clinical Research Excellence Development Scheme. £390,000 *February 2012 – January 2016*
- *Rheumatoid Arthritis and Periodontal Disease (RAPID).* Support for Training and career development of researchers (Marie Curie). Networks for Initial Training. £200,000 S Culshaw, P Garside, I McInnes. October 2012 – September 2015
- *Protein citrullination as a link between periodontal diseases and rheumatoid arthritis and target for development of novel drugs.* European Union FP7 'Health.' Coordinated by University of Goteborg. Total Funding €5,800,000. Allocation to University of Glasgow €544,560. S Culshaw, IB McInnes, P Garside. January 2011 - October 2014

Chapter 3: Clinical Outcomes and Systemic Effects of Periodontal Treatment

3.1 Introduction

The cornerstone of periodontal treatment is non-surgical debridement of the root surface (Badersten *et al.*, 1987, Suvan *et al.*, 2019). The two principle methods of providing this treatment are hand instrumentation and ultrasonic instrumentation. Hand instrumentation involves mechanically removing plaque and calculus deposits from the root surface, usually using specially designed of curettes (Figure 2-1, Chapter 2). Ultrasonic instrumentation is a subset of 'powered instrumentation techniques' and describes the removal of plaque and calculus from the root surface using a rapidly vibrating stainless steel tip connected to a water irrigation system to keep the tip cool and flush debris from the operative site. The ultimate goal of both techniques is biofilm removal. In contemporary daily practice, clinicians often use a combination of these two techniques (Newman *et al.*, 1994), solely due to personal preference or habits formed throughout training. This 'combination/blended approach' may therefore be regarded as 'treatment as normal'.

The clinical effectiveness of non-surgical periodontal therapy has been robustly explored in the periodontal literature. Both hand and ultrasonic instruments have strong evidence (Suvan *et al.*, 2019, Tunkel *et al.*, 2002) to support their ability to reduce local inflammation and promote positive changes in the subgingival environment (Mombelli, 2018) and improved clinical parameters of periodontal disease status (Suvan, 2005).

This study aimed to investigate the clinical and systemic effects of periodontal treatment, comparing different instrumentation techniques.

3.2 Results

3.2.1 Patient Baseline Characteristics

The details of the studies from which the three groups of patients were obtained are described in Chapter 2, under Sections 2.1, Section 2.2 and Figures 2-2, Figure 2-3 and the process of patient selection in Section 2.3.2.

A total of 55 patients were included in the current study and all were diagnosed with Generalised Stage III or Stage IV Periodontitis which was currently unstable (Papapanou *et al.*, 2018). 42 per-cent (23 patients), 11 per-cent (6 patients) and 47 per-cent (26 patients) of study patients were classified as Stage III Grade B, Stage III Grade C and Stage IV Grade C periodontitis respectively.

Visual inspection of the baseline characteristics (Table 3-1) showed more smokers, females and higher baseline PISA in the combination group, relative to hand and ultrasonic groups. However, higher numbers of smokers and baseline disease has potential to affect clinical and systemic inflammatory outcomes of periodontal treatment. As described in Section 2.3.1,, a roughly equal number of patients to the RCT groups were chosen from the cohort study to best match inclusion criteria of the RCT. This led to matching first by medical history as this was deemed most relevant to periodontal disease outcomes (patients were accepted into the cohort study if generally fit and well, but some were taking medication deemed unlikely to impact on antibody responses such as proton pump inhibitors and selective serotonin reuptake inhibitors). By chance, the patients selected from the cohort study often happened to be males who smoke. No statistical testing was carried out for baseline variables in the RCT, as per CONSORT guidelines (http://www.consort-statement.org/). Statistical testing of baseline characteristics is advised against because ‘such significance tests assess the probability that observed baseline differences could have occurred by chance’; however, we already know that any differences are caused by chance as a result of randomization techniques.

Variable Median (Q1,Q3) (min – max)	Hand Instruments (n=19)	Ultrasonic Instruments (n=18)	Combination (n=18)
Age, years	41.3 (39.3, 49) (32 - 59)	46.0 (36.8, 54.4) (32 - 65)	49 (42, 49) (32 – 64)
Gender, female n (%)	9 (47)	10 (56)	1 (6)
Smoking, current n (%)	6 (32)	5 (28)	11 (61)
Current Smoker Pack Years	17 (16.1, 18.8) (15.8 – 19.5)	10.9 (3.0, 17.8) (2.4 - 18)	Data not collected
BMI. Kg/m^2	29.62 (23.8, 34.4) (20 – 39)	27.8 (24.5, 30.0) (21 – 33)	Data not collected
CRP, mg/l	1.21 (0.4, 2.0) (0.3 – 9.9)	1.6 (0.6, 2.5) (0.2 – 7.3)	1.31 (0.7, 2.5) (0.2 – 5.8)
Number of teeth	27 (27.25, 30.8) (24 – 32)	27.5 (24.5, 30) (20 – 32)	29 (26.5, 31) (22 – 32)
PPD (mm)	3.98 (3.11, 4.8) (2.3 – 5.7)	3.70 (3.4, 4.1) (3 – 5.8)	3.74 (3.9 – 4.4) (2.5 – 5.5)
Full mouth BOP (%)	45 (21.3, 69.4) (4.3 – 90.3)	38.1 (21.5, 61.5) (14.7 – 100)	66 (32.3, 81.8) (6 – 100)
Full mouth Plaque (%)	60.5 (25, 67.7) (8.9 – 86.5)	45.9 (26.1, 63.3) (7.4 – 100)	62.5 (45.5, 78.8) (20 – 92)
CAL (mm)	4.4 (3.3, 5) (2.4 – 7.1)	4.1 (3.7, 4.4) (3.2 – 7.5)	4.5 (3.8, 5.4) (3.2 – 6.8)
Pockets ≥5mm (%)	28.9 (18.3, 51.4) (10.7 – 71)	26.7 (22.1, 36.7) (13.1 – 68.9)	29.5 (17.8, 48) (10 – 65)
PISA	1010 (562, 2190) (105.8 – 2914.9)	957.9 (385.6, 1759.6) (305.6 – 3125.6)	1277.5 (730.1, 1837.6) (214.5 – 3655.9)

Table 3-1 - Patient Baseline Characteristics

Baseline patient characteristics. Patients are grouped according to treatment received. All data are displayed as Median (Q1, Q3; min - max)

Normally distributed variables = BMI, number of teeth, PPD, Full mouth BOP, Full mouth Plaque, CAL, Pockets ≥5mm. Non-normally distributed variables = Current Smoker Pack Years, CRP, PISA.

PPD = Periodontal Probing Depth, BOP = Bleeding on Probing, PISA = Periodontally Inflamed Surface Area, CAL = Clinical Attachment Loss, SD = Standard Deviation. BMI = body mass index, CR = C-reactive protein.

3.2.2 Clinical Response to Treatment

Data were interrogated to answer the research question: *'What are the effects on clinical periodontal outcomes, measured 90 days following treatment (comparing baseline with day 90), for each treatment group?'*.

Following treatments (Figure 2-3, Chapter 2), there were consistent improvements in all clinical variables assessed (PISA, PPD, Pockets ≥5mm, BOP, plaque, CAL) in all three treatment groups, both within the RCT groups and the cohort study group. Within group analysis comparing pre vs 90 days post treatment by Wilcoxon Signed Rank test for paired data demonstrated significant improvements (p-values all $p<0.001$) in PISA, PPD, Pockets ≥5mm, BOP, Plaque and CAL for all three groups (Table 3-2 and Figure 3-1). The median periodontal probing depth reduced 0.87 (0.51, 1.38) mm, 1.0 (0.79, 1.31) mm and 0.95 (0.46, 1.36) mm (median (Q1, Q3)) for hand instrumentation, ultrasonic instrumentation and combination instrumentation respectively. Rates of pocket closure were calculated as (defined as conversion of a pocket ≥5 mm to ≤4 mm following treatment) 53.16 (40.0, 77.78) %, 62.54 (50.63, 82.86) % and 70.42 (51.84, 85.69) % (median (Q1,Q3)) for hand instrumentation, ultrasonic instrumentation and combination instrumentation respectively. Bleeding on probing (median (Q1,Q3)) reduced following treatment by 35.00 (10.92, 52.23) % for hand instrumentation; 28.37 (16.17, 49.32) % for ultrasonic instrumentation and 50.5 (28.0, 69.5) % for combination treatment. Plaque scores (median (Q1,Q3)) reduced significantly following treatment in all groups – 44.35 (18.10, 51.66) %, 33.23 (15.21, 48.67) % and 42.0 (27.75, 56.75) % for hand instrumentation, ultrasonic instrumentation and combination instrumentation. Marked reductions in PISA were observed – 936.10 (304.36, 1392.59) mm^2, 743.57 (268.76, 1589.81) mm^2 and 1167.35 (674.52, 1743.58) mm^2 (median, Q1, Q3) for hand instrumentation, ultrasonic instrumentation and combination instrumentation respectively (Table 3-2, Figure 3-1).

The absolute magnitude of change in each clinical parameter was assessed by subtracting Day 90 value from the Baseline value (Table 3-2). Values for magnitude of clinical change were similar in all three groups, with an apparent

trend towards improved outcomes in PISA, pocket closure, CAL and BOP for the combination group.

Table 3-2 – Clinical Parameters of Periodontitis Pre and Post Treatment

Variable *Median (Q1, Q3)*	Timepoint	Hand Instruments (n=19)	Ultrasonic Instruments (n=18)	Combination (n=18)
PISA (mm^2)	Baseline	1010.02 (561.99, 2190.01)	957.93 (385.55, 1759.57)	1277.45 (730.13, 1837.63)
	Day 90	192.59 (59.78, 380.49)	134.85 (62.31, 219.72)	124.20 (58.80, 358.10)
	Change	↓936.10 (304.36, 1392.59)	↓743.57 (268.76, 1589.81)	↓1167.35 (674.53, 1743.58)
	Within group p-value†	<0.001	<0.001	<0.001
PPD (mm)	Baseline	3.98 (3.11, 4.78)	3.70 (3.35, 4.12)	3.74 (3.04, 4.37)
	Day 90	3.02 (2.52, 3.73)	2.68 (2.39, 3.09)	2.77 (2.48, 3.24)
	Change	↓0.87 (0.51, 1.38)	↓1.0 (0.79, 1.31)	↓0.95 (0.46, 1.36)
	Within group p-value†	<0.001	<0.001	<0.001
Pockets ≥5mm (%)	Baseline	28.85 (18.33, 51.39)	26.73 (22.08, 36.71)	29.5 (17.75, 48)
	Day 90	11.67 (3.89, 30.95)	10.88 (3.87, 16.88)	10.00 (3.50, 12.25)
	Change	↓17.30 (11.29, 23.21)	↓16.87 (12.83, 25.69)	↓16.5 (12.0, 34.75)
	Within group p-value†	<0.001	<0.001	<0.001
Full Mouth BOP (%)	Baseline	45.0 (21.26, 69.44)	38.11 (21.45, 61.49)	66 (32.25, 81.75)
	Day 90	8.33 (2.98, 13.10)	8.10 (4.12, 12.08)	8.5 (3.75, 18.00)
	Change	↓35.00 (10.92, 52.23)	↓28.37 (16.17, 49.32)	↓50.5 (28.0, 69.5)
	Within group p-value†	<0.001	<0.001	<0.001
Full Mouth Plaque (%)	Baseline	60.48 (25.0, 67.74)	45.92 (26.1, 63.33)	62.5 (45.5, 78.75)
	Day 90	8.33 (4.17, 14.06)	7.80 (3.50, 13.25)	13.00 (7.75, 28.5)
	Change	↓44.35 (18.10, 51.66)	↓33.23 (15.21, 48.67)	↓42.0 (27.75, 56.75)
	Within group p-value†	<0.001	<0.001	<0.001
CAL (mm)	Baseline	4.36 (3.29, 5.02)	4.14 (3.66, 4.43)	4.51 (3.8, 5.38)
	Day 90	4.01 (3.03, 4.68)	3.63 (3.10, 4.12)	3.42 (2.81, 4.14)
	Change	↓0.36 (0.05, 1.12)	↓0.52 (0.26, 0.80)	↓1.03 (0.72, 1.51)
	Within group p-value†	<0.001	<0.001	<0.001

†Differences between baseline and day 90 within groups tested using Wilcoxon signed rank test.

(Table legend overleaf)

Table 3-2 – Clinical Parameters of Periodontitis Pre and Post Treatment

Clinical measures of periodontitis disease state for baseline and Day 90 following treatment.

Patients are grouped according to treatment received.

Magnitude of improvement in clinical measures of periodontitis disease state following treatment are shown in the 'Change' row.

All data are presented as Median (Q1, Q3) and are relative to baseline measurements, apart from pocket closure % (defined as percentage of pockets being converted from ≥5mm probing depth to ≤4mm probing depth following treatment).

Arrows denote direction of change – calculated by subtracting pre-treatment value of variable from post treatment value.

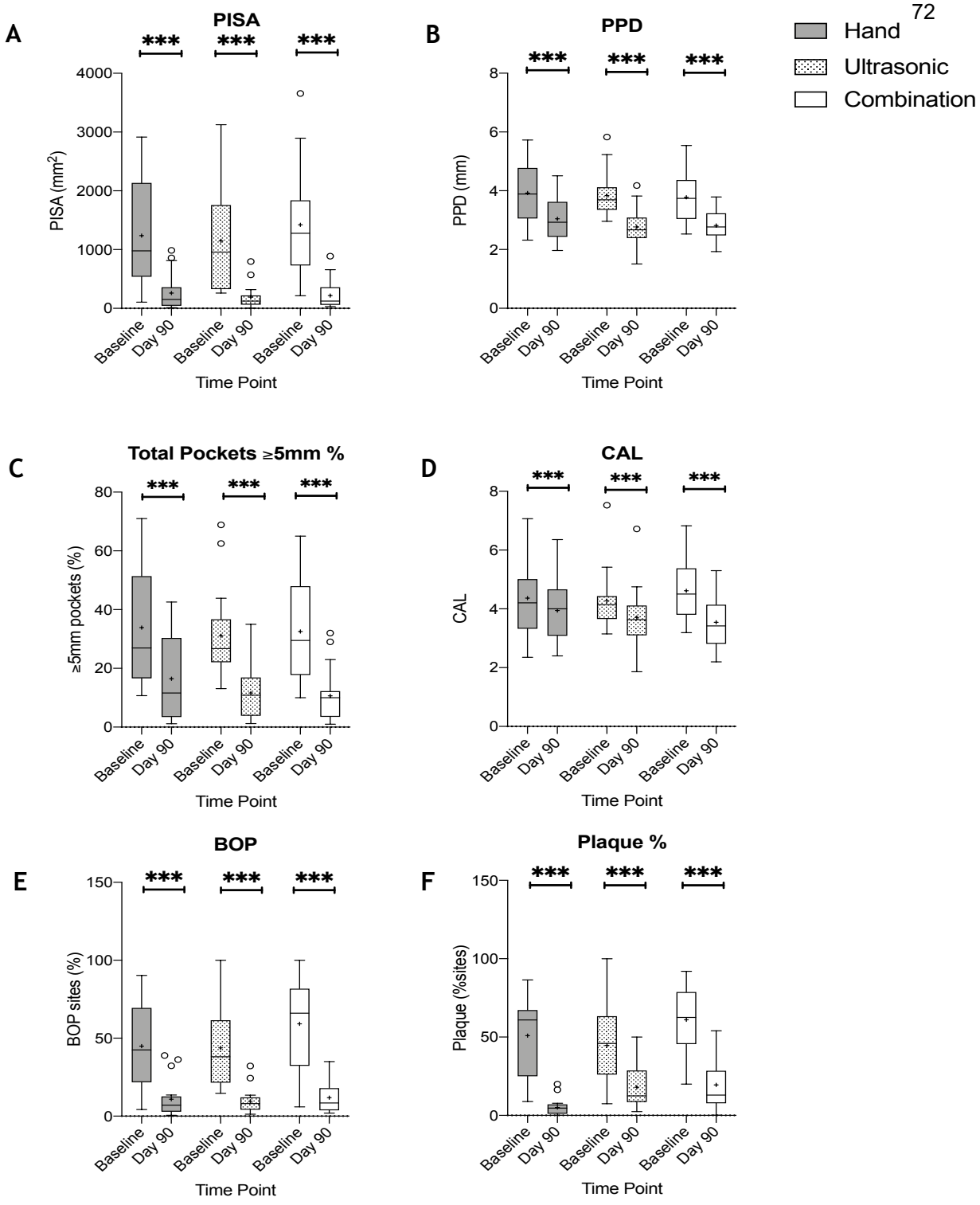

Figure 3-1 - Clinical Outcomes of Periodontal Treatment

Patients were treated with exclusively hand instruments (grey bars, n = 19), exclusively ultrasonic instruments (dotted bars, n = 18) or a combination of both instruments (white bars n = 18). PISA was recorded before and 90 days after treatment.

**** = p<0.001 comparing pre and post treatment within each group by Wilcoxon Signed Rank Test for related samples. Data are presented as Tukey Box Plots (horizontal bar shows median, + shows mean, whiskers show minimum and maximum and circles show outliers as separate data points).*

A - PISA; B - PPD; C - Total Pockets ≥5mm; D - CAL; E - BOP; F - Plaque

3.2.3 Clinical response between treatment groups and the effect of confounding variables

To address the research questions of 'Is there a difference in clinical outcome between treatment groups?' and 'How is clinical outcome affected by particular key confounders?', a data modelling approach was adopted.

As detailed in Section 2.3.7 (Chapter 2), General Linear Models were devised to investigate the effect of different treatment groups on clinical outcomes considering confounding variables of relevance to periodontal disease and its treatment – such as smoking status, level of baseline disease and number of teeth. The most basic model included no confounders. Models were then created incorporating baseline levels of disease and sequentially more confounding variables. Parameter estimates (ß values) between treatment groups were used to assess the impact such variables had on clinical outcomes, relative to the preceding model. Parameter estimates (ß values) represent the change in standard deviations of an outcome variable (e.g. periodontal pocket depth) when a one standard deviation change is made to the predictor variable. ß values were used as a means to help quantify the effect confounders had upon the outcome of interest (when compared to the preceding model's parameter estimate value). Due to the variety of variables and multiple variables using Ln data (all but PPD and CAL), a universally applicable 'clinically relevant' change in ß value cannot be suggested.

Table 3-3 reports the findings from the General Linear Models described in Section 2.3.7 and compared the two arms of the RCT in the first instance, then compared across the three treatment groups. There is little difference between the two groups in the RCT nor the three groups in the combined study for any of the follow-up clinical measures for Model 1 (unadjusted). These differences did not alter after adjustment for baseline measures or any of the relevant confounding variables (Models 2 – 5). The exception was for CAL (clinical attachment level). However, this is likely to be a spurious result - as more stringent modelling (Models 3, 4 and 5) did not repeat this finding consistently.

Model 2 (Table 3-3) was adjusted for baseline levels of disease. ß values for the difference between treatment groups were minimally affected. For example, when considering PISA, the parameter estimates (ß values) of hand instrumentation vs ultrasonic instrumentation and hand instrumentation vs combination instrumentation increased by 0.026 and 0.186 respectively (with respect to the ß value when using the unadjusted model) (Table 3-3). Overall, relative changes in parameter estimates (Ln transformed data) were in the region of 0.006 to 0.140 across all clinical variables assessed when baseline levels of disease were included in modelling. This analysis suggests minimal differences in clinical outcomes between treatment groups when baseline disease severity was taken into account.

A greater change in parameter estimate was demonstrated when further adjustment was made for smoking status (Model 3), particularly comparing hand instrumentation and combination instrumentation. For total pockets ≥5mm, ß increased from -0.372 to 0.793 – a change of 1.165. When adjusting for levels of smoking, parameter estimates for all clinical variables changed with greatest magnitude, compared to any other confounder. This effect was most apparent in the combination group. This analysis suggests smoking was the most influential confounding factor for treatment outcome within the current study and the finding of the greatest effect in the combination group may relate to the comparatively higher number of smokers, compared to other groups.

When further adjusting for treatment time, parameter estimate changes were noted in the region of 0.004 to 0.200 across all clinical variables considered. With further adjustments for age, gender, and number of teeth, similar, low magnitude changes were noted across all clinical variables (Table 3-3). These low magnitude changes were similar across all treatment groups and in real terms suggests a minimal, likely negligible influence of these confounding factors on clinical outcomes factors.

There were similar clinical outcomes (pre vs post treatment) (indicated by PISA, PPD, pockets ≥5mm, BOP, plaque, CAL) in all groups, assessed by fully adjusted general linear model - all p values >0.05 (Table 3-3). However, caution is

advised in interpretation of this finding as both the RCT and the current study were not specifically powered to detect differences or equivalence in clinical variables.

In summary, results would suggest smoking had the greatest effect on differences between treatment groups, for the majority of clinical variables – compared to other confounders. This result is expected as it is well reported smoking is a significant factor in clinical response to periodontal treatment. This effect was most apparent within the combination treatment group - this group had the greatest number of patients who smoke and may explain therefore this result.

Table 3-3 – Clinical Outcomes Between Treatment Groups

	Model 1	Model 2	Model 3	Model 4	Model 5
PISA					
Hand	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)
Ultrasonic ß (95% CI)	-0.164 (-0.942 to 0.613)	-0.138 (-0.783 to 0.507)	0.070 (-1.100 to 1.240)	0.076 (-1.117 to 1.269)	-0.074 (-1.585 to 1.436)
Combination ß (95% CI)	-0.031 (-0.808 to 0.747)	-0.217 (-0.867 to 0.432)	0.788 (-1.452 to 3.028)	0.786 (-1.481 to 3.053)	1.099 (-1.438 to 3.635)
p-value (H vs U)	0.691	0.676	0.791	0.406	0.593
p-value (H vs U vs C)	0.905	0.793	0.946	0.963	0.856
PPD*					
Hand	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)
Ultrasonic ß (95% CI)	-0.277 (-0.703 to 0.149)	-0.225 (-0.481 to 0.032)	-0.172 (-0.631 to 0.288)	-0.144 (-0.610 to 0.322)	-0.208 (-0.793 to 0.377)
Combination ß (95% CI)	-0.231 (-0.701 to 0.151)	-0.143 (-0.399 to 0.114)	0.343 (-0.532 to 1.219)	0.333 (-0.546 to 1.212)	0.302 (-0.664 to 1.268)
p-value (H vs U)	0.179	0.099	0.138	0.246	0.095
p-value (H vs U vs C)	0.378	0.212	0.247	0.418	0.394
Total pockets≥5mm					
Hand	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)
Ultrasonic ß (95% CI)	-0.237 (-0.935 to 0.461)	-0.230 (-0.760 to 0.299)	-0.034 (-0.999 to 0.932)	0.053 (-0.920 to 1.026)	-0.080 (-1.602 to 1.442)
Combination ß (95% CI)	-0.400 (-1.098 to 0.298)	-0.372 (-0.901 to 0.158)	0.793 (-1.054 to 2.641)	0.748 (-1.094 to 2.589)	1.075 (-1.481 to 3.630)
p-value (H vs U)	0.297	0.265	0.309	0.279	0.104
p-value (H vs U vs C)	0.515	0.368	0.694	0.837	0.636

(continued)

Table 3-3 continued

	Model 1	Model 2	Model 3	Model 4	Model 5
Full Mouth BOP %					
Hand	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)
Ultrasonic ß (95% CI)	0.053 (-0.572 to 0.677)	-0.005 (-0.521 to 0.511)	0.010 (-0.930 to 0.950)	-0.014 (-0.972 to 0.944)	-0.183 (-1.393 to 1.027)
Combination ß (95% CI)	0.184 (-0.440 to 0.809)	-0.085 (-0.612 to 0.441)	0.575 (-1.279 to 2.428)	0.589 (-1.285 to 2.463)	0.675 (-1.406 to 2.756)
p-value (H vs U)	0.869	0.946	0.917	0.687	0.687
p-value (H vs U vs C)	0.832	0.937	0.979	0.954	0.715
Full Mouth Plaque %					
Hand	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)
Ultrasonic ß (95% CI)	-0.082 (-0.841 to 0.677)	0.006 (-0.732 to 0.743)	-0.240 (-1.568 to 1.089)	-0.439 (-1.707 to 0.829)	-0.248 (-1.949 to 1.452)
Combination ß (95% CI)	0.335 (-0.424 to 1.093)	0.176 (-0.571 to 0.923)	0.199 (-2.279 to 2.678)	0.141 (-2.205 to 2.488)	0.223 (-2.580 to 3.025)
p-value (H vs U)	0.804	0.910	0.865	0.371	0.396
p-value (H vs U vs C)	0.518	0.873	0.980	0.541	0.595
CAL*					
Hand	0 (reference)	0 (reference)	0 (reference)	0 (reference)	0 (reference)
Ultrasonic ß (95% CI)	-0.246 (-0.895 to 0.403)	-0.136 (-0.477 to 0.206)	0.038 (-0.577 to 0.654)	0.030 (-0.601 to 0.661)	-0.072 (-0.861 to 0.717)
Combination ß (95% CI)	-0.413 (-1.062 to 0.236)	-0.571 (-0.913 to -0.228)	-0.459 (-1.61 to 0.688)	-0.461 (-1.622 to 0.699)	-0.228 (-1.531 to 1.075)
p-value (H vs U)	0.467	0.459	0.508	0.595	0.125
p-value (H vs U vs C)	0.443	0.004	0.082	0.111	0.194

Table legend overleaf

Table 3-3 – Clinical Outcomes Between Treatment Groups - General Linear Modelling

Parameter estimates with 95% confidence intervals and p -values for ultrasonic instrumentation compared with hand instrumentation, compared with combination treatment following treatment.

Hand Instrumentation Group = reference group for General Linear Modelling

Model 1: Unadjusted

Model 2: Adjusted for baseline levels of clinical variable

Model 3: Adjusted for baseline levels of clinical variable and smoking status

Model 4: Adjusted for baseline levels of clinical variable, smoking status, treatment time,

Model 5: Adjusted for baseline levels of clinical variable, smoking status, treatment time, age, gender, number of teeth.

*Ln data used throughout unless denoted by *, in which case non-transformed data used*

Categorical variables (treatment group, smoking status, gender) assigned as Fixed Factors

Continuous variables (clinical variables [baseline and day 90], treatment time, number of teeth) assigned as Covariates

3.2.4 Treatment Time in Hand vs Ultrasonic treatment groups

Previous studies document faster treatment with ultrasonic instruments (Tunkel *et al.*, 2002, Laurell, 1990, Yukna *et al.*, 1997, Breininger *et al.*, 1987). Therefore, the research question '*Are there differences in the time taken for treatment according to treatment group?*' was considered by the following analysis. The time to complete treatment was evaluated by measuring the time spent instrumenting the tooth and root surfaces, measured from the point of first contact of an instrument onto a tooth/root surface. Data for precise time of instrumentation were available only for hand and ultrasonic groups; comparable data were not available for the combination treatment group. The data were normally distributed in both groups.

The total treatment time was less using ultrasonic instruments alone compared with using hand instruments alone (Figure 3-2). The Mean (SD) treatment time for hand instrumentation was 96.9 (23.08) minutes. The Mean (SD) treatment time for ultrasonic instrumentation was 75.39 (17.82) minutes. This reduction was shown to be statistically significant by independent sample 2 tailed t-test ($p<0.003$ (mean difference: 21.51 minutes; 95% CI 9.22 to 34.62)). Ultrasonic instrumentation required less time to complete treatment in this study. Ultrasonic instrumentation treatment time had a narrower range of values compared to hand instrumentation, as suggested by its marginally lower standard deviation.

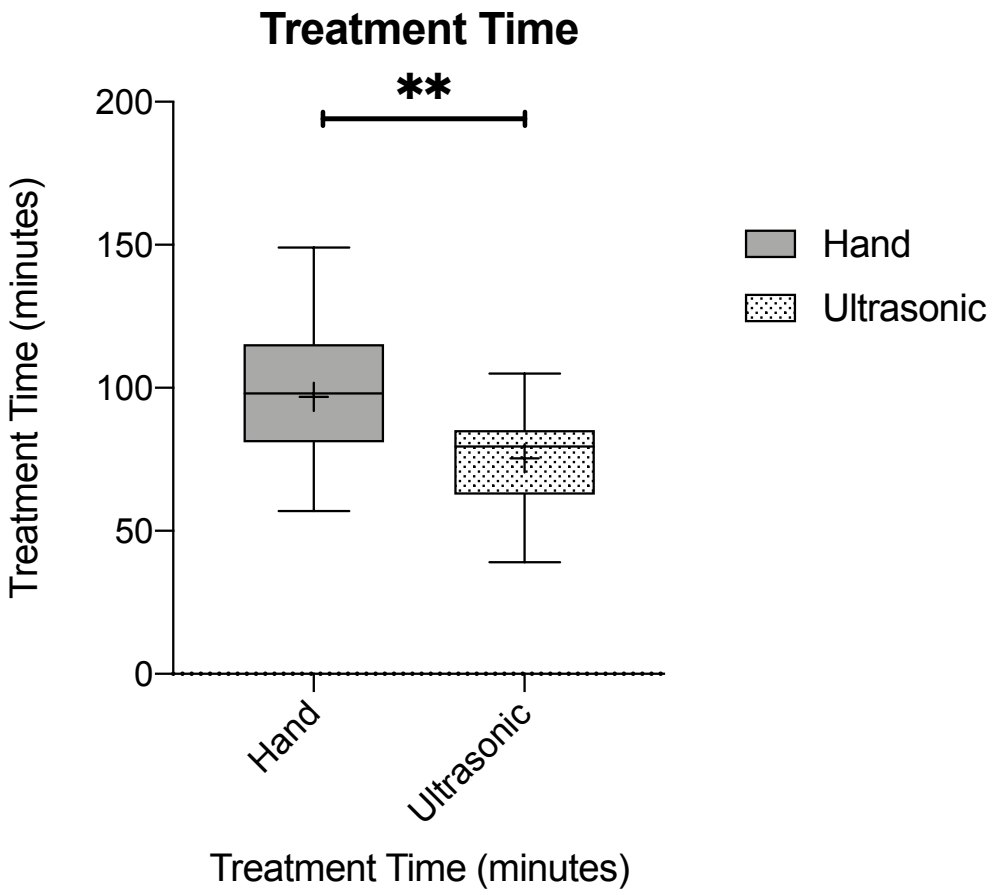

Figure 3-2 - Treatment Time

*Patients were treated with exclusively hand instruments (grey bar, n = 19), exclusively ultrasonic instruments (dotted bar, n = 18). Data for combination treatment were not available. Box and whisker plot displaying values for time taken to complete periodontal instrumentation, measured in minutes, with respect to instrumentation technique. Mean (+), median, Q1, Q3, Min and Max data are presented. ** = p<0.01 (95% CI 9.22 – 34.62) by independent sample t-test*

To investigate the interaction of treatment time and disease severity (ie PISA), the data were subgrouped by instrumentation type and separate correlation coefficients (Pearson) were calculated. A Scatter plot was produced to show the association graphically. Hand instrumentation treatment time correlated positively with disease severity (r=0.62) whereas there was a less pronounced relationship between disease severity and treatment time using ultrasonic instruments (r=0.33). Similarly, time taken for hand instrumentation correlated with the proportion of pockets ≥5mm (Figure 3-3B) (r=0.76). Correlation between proportion of pockets ≥5mm and time taken to complete ultrasonic debridement (Figure 3-3) was r=0.271. Ultrasonic treatment therefore, on average, required less time to complete treatment than hand instrumentation, and the time saving with ultrasonic use appears proportionally greater for more severe disease; however, this conclusion is based on a subgroup analysis, with inherent limitations.

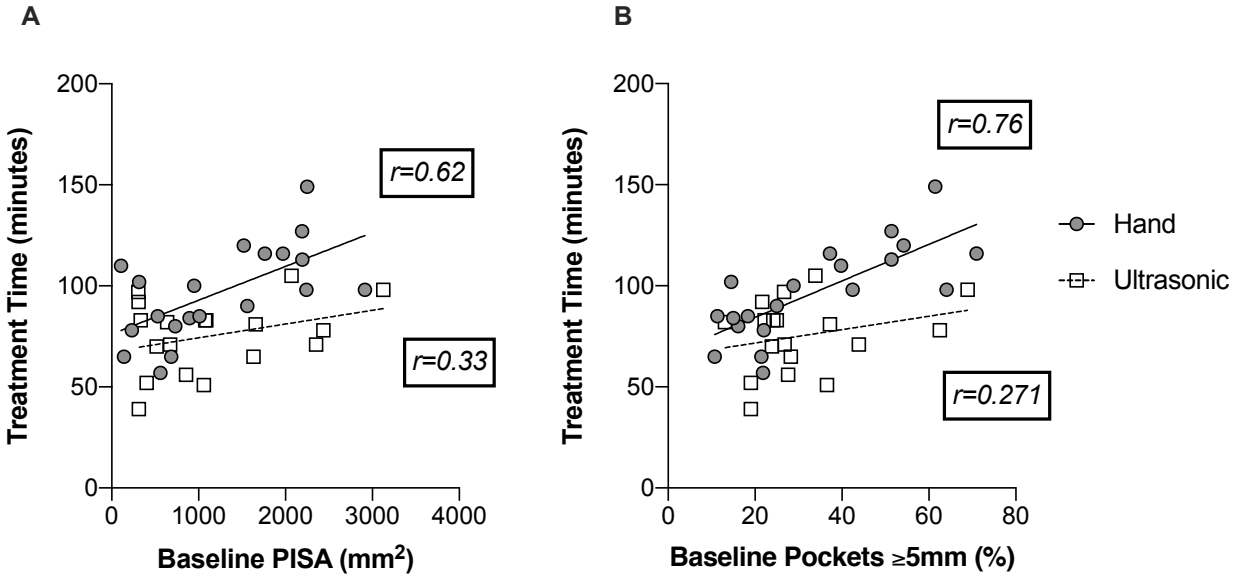

Figure 3-3 - Treatment Time vs Baseline Severity of Inflammation

Patients were treated with exclusively hand instruments (grey dots, n = 19), exclusively ultrasonic instruments (white squares, n = 18). Data for treatment time for combination treatment was not available.

Scatter plot of Baseline Disease Severity (measured by Baseline PISA) vs Treatment time and Baseline Pockets ≥5mm. *Each dot represents a single patient.*

Lines of best fit are illustrated.

3.2.5 Measures of Clinical Success

Clinical results observed within the current study were then considered in the context of published criteria of 'success' in periodontal treatment and address the research question 'Was treatment for study patients successful in the context of published criteria of a successful outcome of periodontal treatment?' A literature search was carried out to identify published criteria used to assess the clinical 'success' of periodontal therapy. In clinical practice, clinical outcomes in periodontal therapy are objectively measured using parameters such as PPD, pocket closure rates, plaque scores and bleeding on probing scores. Criteria were chosen for inclusion if the criteria were published in peer reviewed journals, and the parameters they used were in regular clinical use within our institution.

The number of patients in each treatment group who fulfilled all or part of the different published criteria varied considerably depending on the criteria (Table 3-4). No patients in any treatment group fulfilled the SDCEP (Scottish Dental Clinical Effectiveness Programme, 2014), criteria in full. The 'all sites PPD <4mm' goal was not met by any patient, whereas a plaque percentage of <10% was achieved by over 50% of patients in all groups. For other success criteria, just over half of all patients achieved 57% pocket closure (Suvan, 2019); 38% achieved the <25% BOP and <8 sites of PPD ≥5mm (Lang and Tonetti, 2003); only 16% achieved ≤4 sites with PPD ≥5mm (Feres). When evaluating BOP at a 10% threshold, there appeared to be differences between the groups with eleven patients achieving this criterion in the combination group, but only two in the hand instrument group and none in the ultrasonic group. Otherwise, there were no clear differences between the groups (Table 3-4). Mean pocket closure values were similar in the current study to the most recent systematic review on the subject of periodontal treatment outcomes. Overall the data indicate reduction in PPD as the most challenging aspect to achieve, with plaque and BOP values being more readily attainable for patients in this study. It should be noted that the patients in this study in some cases received further specialist treatment – the data evaluated are following initial non-surgical treatment only.

To visually assess how individual study patients performed with respect to success criteria, a schematic was created to categorise patients dichotomously into ‘responder’ or ‘non-responder’ status (Figure 3-4). Some additional ‘success’ criteria ((Hughes *et al.*, 2006), (Bizzarro *et al.*, 2016), (Eick *et al.*, 2017),(Greenwood *et al.*, 2020)) are included in Figure 3-4. Unlike those in Table 3-4, these additional criteria have not been widely adopted clinically. However, they were included to provide further points of reference to assess outcomes in the current study. There was clear variability in responder status when comparing published success criteria, evaluated by individual patient. All patients fulfilled Greenwood 2020 (Greenwood *et al.*, 2020) and no patients fulfilled pocket depth criteria from SDCEP (Scottish Dental Clinical Effectiveness Programme, 2014) (Figure 3-4).

Success Criteria	Constituents of Success Criteria	Hand Instrumentation (n=19)	Ultrasonic Instrumentation (n=18)	Combination Instrumentation (n=18)	Total Fulfilling All Criteria* (n= 55)
Feres	*≤4 sites with PPD ≥5mm*	2	3	4	9 (16%)
Lang and Tonetti	*<8 sites of PPD ≥5mm*	7	5	4	21 (38%)
	<25% BOP	17	17	16	
Suvan	*Mean 57% pocket closure*	9	10	12	31 (55%)
SDCEP	*Plaque <15%*	16	15	11	0 (0%)
	BOP <10%	2	0	11	
	All sites <4mm PPD	0	0	0	

Table 3-4 – Measures of Clinical Success following Periodontal Treatment Overview

Number of patients from respective treatment arms of the current analysis achieving aspects of published periodontal clinical success criteria.

Published criteria of 'success' following treatment for periodontal disease:

Feres 2020 (Feres et al., 2020)

Lang and Tonetti 2003 (Lang and Tonetti, 2003) (modified)

Suvan 2019 (Suvan et al., 2019)

Scottish Dental Clinical Effectiveness Programme 2014 (Programme, 2014)

**Full study data set*

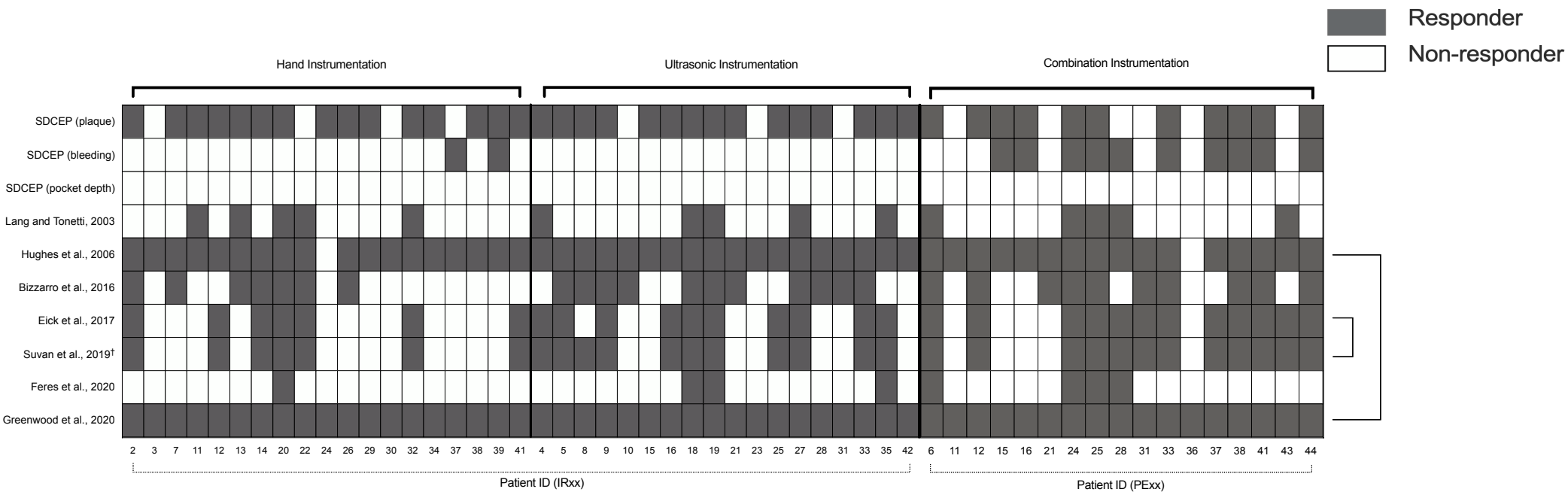

Figure 3-4 – Measures of Clinical Success following Periodontal Treatment

Schematic representation of patients (separated by study) within the current analysis assessed against published periodontal clinical success criteria.

Connecting lines across the right y-axis associate published criteria inspired by one another.

Each column represents a single patient. If a patient is a 'Responder' with respect to the success criteria, a shaded rectangle is shown. Individual patient response status across criteria can be assessed by following y-axis.

Published criteria of 'success' following treatment for periodontal disease:

Feres 2020 (Feres et al., 2020) - ≤4 sites with PPD ≥5mm; Lang and Tonetti 2003 (Lang and Tonetti, 2003) (modified) - <8 sites of PPD ≥5mm and <25% BOP; Suvan 2019 (Suvan et al., 2019) - Mean 57% pocket closure; Scottish Dental Clinical Effectiveness Programme 2014 (Programme, 2014) - Plaque <15%, BOP <10%, All sites <4mm PPD; Hughes 2006 (Hughes et al., 2006) - ≥30% responding sites. Responding sites are those ≥5mm at BL which decreased by 2mm; *Eick 2017 (Eick et al., 2017)* - 60% reduction in pockets >4mm; *Greenwood 2020 (Greenwood et al., 2020)* - ≥25% responding sites. Responding sites are those ≥5mm at BL which decreased by 2mm; *Bizarro 2016 (Bizzarro et al., 2016)* - Above median pocket closure rate

3.2.6 Effect of periodontal treatment on systemic inflammation

In addition to exploration of clinical outcomes of periodontal treatment, the systemic effects were considered by evaluating serum hsCRP. Specific research questions considered included 'Does CRP immediately increase following periodontal treatment?' and 'Is there a difference between treatment groups with respect to changes in CRP levels at day 90 post-treatment?' The immediate post treatment change in CRP was only evaluated in the RCT, therefore there were no data for immediate changes in CRP in the combination group.

Serum CRP was evaluated at baseline, day 1, day 7 and day 90 in the RCT, and at baseline and day 90 in the cohort study (Figure 2-3, Chapter 2). Serum CRP increased significantly at Day 1 following treatment across all patients in hand and ultrasonic treatment groups (Table 3-5 and Figure 3-5, Wilcoxon Signed Rank Test, 2-tailed p value = 0.008) compared to baseline levels.

Following the increase at Day 1, serum CRP in both hand and ultrasonic instrumentation groups reduced, initially at Day 7 and further at Day 90 to approximately baseline levels (Figure 3-5). Changes in CRP levels in hand vs ultrasonic treatment groups were of a comparable, albeit low, magnitude (Table 3-5). Median (Q1,Q3) CRP for the hand instrumentation group reduced by 0.06 (-0.56, 0.48). Median (Q1,Q3) CRP for the ultrasonic instrumentation group reduced by 0.15 (-0.07, 1.29) and median (Q1,Q3) CRP for combination treatment increased by 0.08 (-0.72, 0.41) at Day 90 follow up.

The magnitude of differences in CRP measured at Day 90 between treatment groups was minimal (Table 3-5). Across all patients, at Day 90 follow up, CRP levels were not significantly different compared to baseline (by performing paired t-test using Ln transformed data; mean difference = 0.216; p = 0.085, 95% CI = -0.03 to 0.46).

Furthermore, following adjustment for baseline levels of CRP, sex, age, smoking status, BMI at baseline and treatment time, in a multivariable model no

statistically significant differences were observed between treatment groups (p=0.125) (Table 3-6). This absence of difference is also seen in separate general linear modelling, comparing hand and ultrasonic treatment groups in isolation (p=0.28, 95% CI -0.259 to -0.867). The 95% confidence interval for this finding demonstrates a fairly imprecise result. These results therefore suggest some minor variation in changes in CRP ninety days following periodontal treatment, across the three treatment groups. Caution in interpretation is warranted due to lack of specific statistical powering for differences in CRP at day 90.

INSTRUMENTATION TECHNIQUE	HAND INSTRUMENTS	ULTRASONIC INSTRUMENTS	COMBINATION
BASELINE	1.21 (0.44, 2.03)	1.60 (0.62, 2.49)	1.31 (0.69, 2.47)
DAY 1	1.78 (0.99, 3.96)	2.57 (1.02, 3.86)	No Data
DAY 7	1.88 (0.71, 3.20)	0.97 (0.51, 2.74)	No Data
DAY 90	1.28 (0.54, 2.34)	0.72 (0.44, 1.12)	1.36 (0.58, 2.55)
CRP CHANGE PRE VS 90 DAYS POST TREATMENT	↓0.06 (-0.56 – 0.48)	↓0.15 (-0.07, 1.29)	↑0.08 (-0.72, 0.41)

Table 3-5 – Serum C-reactive Protein (mg/L)

Patients were treated with exclusively hand instruments (n = 19), exclusively ultrasonic instruments (n = 18) or a combination of both instruments (n = 18).
Median (Q1, Q3) data are displayed, as data were non-normally distributed.
C-reactive protein titre is displayed at each study time point. Reduction in CRP is also shown – please note no statistical tests were carried out using change data.

Table 3-6: Parameter estimates with 95% confidence intervals for inter-group differences for ln-transformed serum C-reactive Protein at day 1, day 7 and day 90.

		Day 1			Day 7			Day 90		
		Β	**95% CI**	**p-value**	**Β**	**95% CI**	**p-value**	**Β**	**95% CI**	**p-value**
C-Reactive protein (Hand instruments vs Ultrasonic Instruments)										
Model 1†		0.143	-0.582 to 0.867	0.69	0.271	-0.553 to 1.09	0.51	0.518	-0.202 to 1.239	0.15
Model 2‡		0.130	-0.369 to 0.628	0.60	0.311	-0.329 to 0.950	0.33	0.482	-0.073 to 1.038	0.09
Model 3§		0.293	-0.221 to 0.810	0.30	0.231	-0.510 to 0.972	0.53	0.304	-0.259 to 0.867	0.28
C-Reactive protein (Hand instruments vs Ultrasonic Instruments vs Combination Instruments)										
Model 1†	Hand	-	-	-	-	-	-	0 (ref)	0 (ref)	
	Ultrasonic	-	-	-	-	-	-	-0.518	-1.231 to 0.195	0.239
	Combination	-	-	-	-	-	-	0.032	-0.671 to 0.734	
Model 2‡	Hand	-	-	-	-	-	-	0 (ref)	0 (ref)	
	Ultrasonic	-	-	-	-	-	-	-0.480	-1.019 to 0.058	0.141
	Combination	-	-	-	-	-	-	-0.012	-0.542 – 0.519	
Model 3§	Hand	-	-	-	-	-	-	0 (ref)	0 (ref)	
	Ultrasonic	-	-	-	-	-	-	-0.335	-1.462 to 0.792	0.125
	Combination	-	-	-	-	-	-	0.958	-0.863 to 2.780	

Table legend overleaf

Table 3-6: Parameter estimates with 95% confidence intervals for inter-group differences for ln-transformed serum C-reactive Protein at day 1, day 7 and day 90.

Results of General Linear Modelling comparing levels of serum CRP across treatment groups as indicated at follow up time points, explored within three models.

No data available for Day 1 or Day 7 CRP levels for combination treatment.

'-' denotes no available data.

[†]Model 1: Unadjusted.
[‡]Model 2: Adjusted for baseline levels of CRP.
[§]Model 3: Adjusted for baseline levels of CRP, sex, age, smoking status, BMI at baseline (only used for RCT data as not collected for cohort study) and treatment time.

β-values are on the ln-transformed scale

Categorical variables (sex, age, smoking status) assigned as fixed factors
Continuous variables (CRP, BMI at baseline, treatment time) assigned as covariates

Hand instrumentation assigned as reference variable for all testing

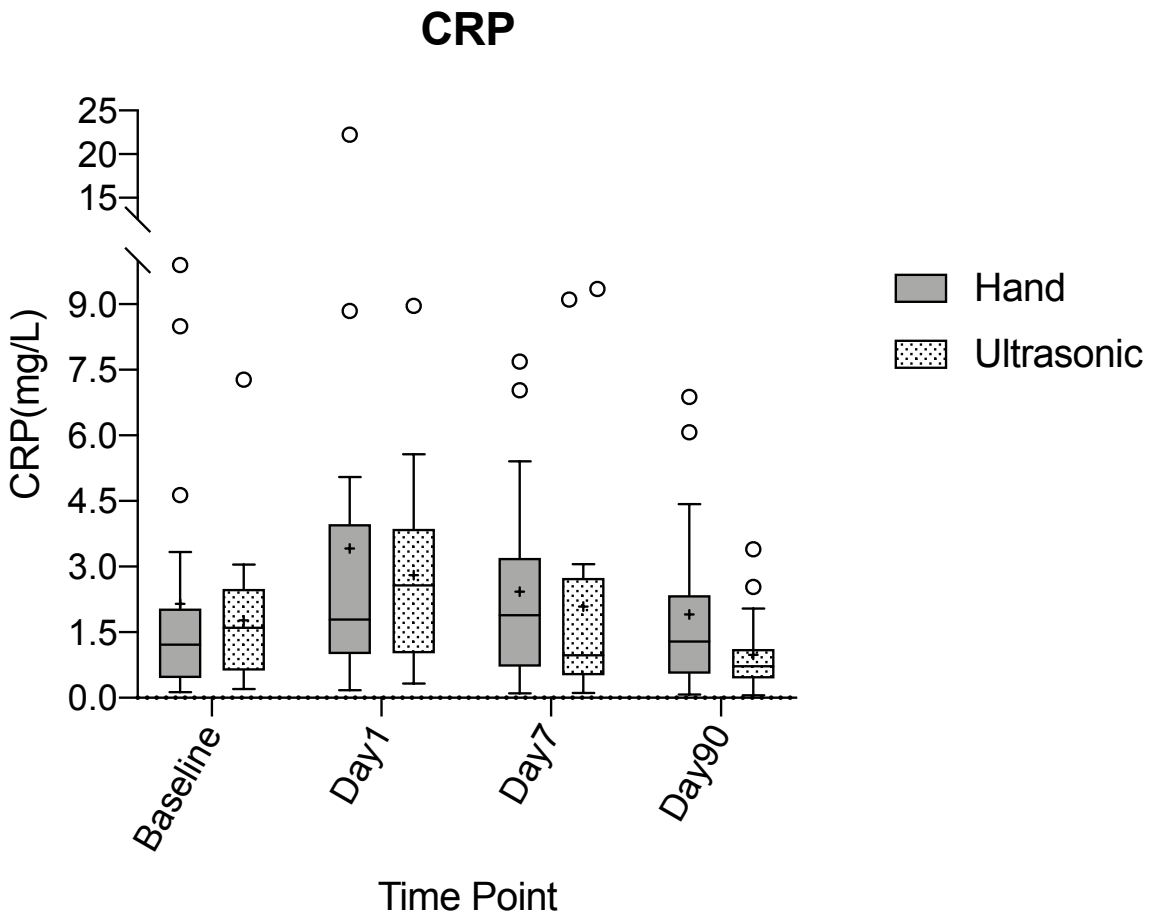

Figure 3-5 - Changes in Serum C-reactive Protein at day 1, day 7 and day 90 following treatment

Patients were treated with exclusively hand instruments (grey, n = 19) or exclusively ultrasonic instruments (dotted, n = 18). Box and whisker plot displaying values for CRP titre across all study time points.

Data are presented as Tukey Box Plots (horizontal bar shows median, + shows mean, whiskers show minimum and maximum and circles show outliers as separate data points.

Please see Table 3-5 for raw data

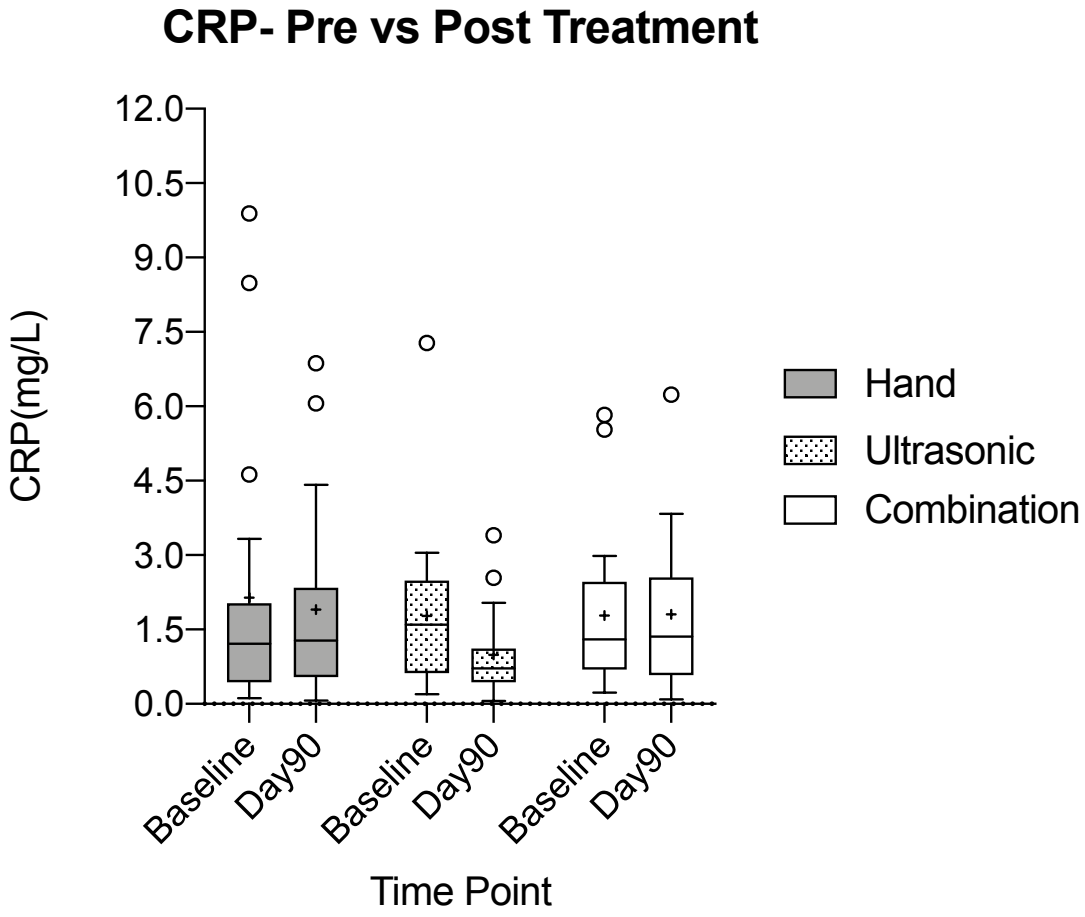

Figure 3-6 – Serum C-reactive Protein at baseline and 90 days post treatment

Patients were treated with exclusively hand instruments (grey bars, n = 19), exclusively ultrasonic instruments (dotted bars, n = 18) or a combination of both instruments (white bars n = 18).

Box and whisker plot displaying values for CRP titre with respect to instrumentation technique.

Data are presented as Tukey Box Plots (horizontal bar shows median, + shows mean, whiskers show minimum and maximum and circles show outliers as separate data points.

Please see Table 3-5 for raw values

3.3 Discussion

The data presented in this chapter show periodontal treatment, regardless of instrumentation approach, resulted in significant clinical improvements. Previous studies have compared hand and ultrasonic, but few have included any comparison with 'blended' or 'combination' approaches – the latter being the most commonly used in clinical practice.

The data demonstrate that systemic inflammation - evaluated by serum hsCRP - increases one day following full mouth debridement, irrespective of instrument choice; and that serum CRP serum returned to approximately baseline levels at day 90 following treatment. No differences were observed in day 90 levels of CRP comparing treatment groups.

Non-surgical periodontal treatment clinical effectiveness was recently assessed in a systematic review (Suvan *et al.*, 2019) which analysed 18 studies across a trio of 'PICO' questions – one of which involved the comparison of hand and ultrasonic instruments for subgingival instrumentation in the context of generalised periodontitis. This systematic review found no statistically significant differences between the two techniques, with a weighted periodontal probing depth reduction of 1.7 mm at approximately 6 months follow up (for combination treatment; 11 studies analysed). The current study reported median (Q1,Q3) periodontal probing depth changes of 0.87 (0.51, 1.38) mm, 1.0 (0.79,1.31) mm and 0.95 (0.46, 1.36) mm for hand instrumentation, ultrasonic instrumentation and combination instrumentation respectively. This observed difference between the data presented here and the systematic review may relate to follow up periods differing between 90 days (current study) and 6 months (systematic review). This difference may be significant as it has been established collagen maturation and further reduction in periodontal probing depth has potential to continue over at least a 6-month period (Stanton *et al.*, 1969) – with the effect of gaining further clinical improvements. There may also be variations in population studied, baseline disease severity or data collection methods. Overall, it seems most likely that a follow up of 90 days may be too

soon to assess definitive changes in mean periodontal probing depths following non-surgical periodontal therapy.

With respect to clinical attachment level (CAL), the current study showed a significant improvement following treatment with all treatment approaches ($p<0.01$) (Figure 3-1F) and a CAL change (median (Q1,Q3) shown) of 0.36 (0.05, 1.12) mm, 0.52 (0.26, 0.80) mm and 1.03 (0.72, 1.51) mm for hand instrumentation, ultrasonic instrumentation and combination treatment respectively. A recent systematic review on efficacy of non-surgical periodontal treatment (Smiley *et al.*, 2015) reported a mean CAL change of approximately 0.5mm following treatment, similar to the current study's findings.

In the current study, plaque and bleeding on probing both significantly reduced following all treatments provided, with median (Q1,Q3) reductions in plaque of 44.35 (18.10, 51.66) %, 33.23 (15.21, 48.67) % and 42.0 (27.75, 56.75) % and median (Q1, Q3) reductions in bleeding on probing of 35.00 (10.92, 52.23) %, 28.37 (16.17, 49.32) % and 50.5 (28.0, 69.5) % for hand instrumentation, ultrasonic instrumentation and combination instrumentation respectively. This is again in line with published evidence on the expected clinical outcomes following non-surgical periodontal therapy of an overall reduction in percentage of sites exhibiting bleeding on probing and improvements in full mouth plaque scores (Smiley *et al.*, 2015, Suvan *et al.*, 2019).

Smoking was shown as the most influential confounder with respect to effects on clinical periodontal parameters in the current study. This effect was most notable for treatment using combination instruments (Table 3-3). An explanation of this finding is likely the comparatively high number of smokers in this treatment group. However, the finding of smoking having a large effect upon clinical parameters is in line with published evidence (Bergstrom *et al.*, 1991, Bergstrom *et al.*, 2000, Haffajee and Socransky, 2001, Leite *et al.*, 2018). Notably fewer females were present in the combination group compared to other groups studied (Table 3-1). When adjusting for Gender (with age and number of teeth), minimal parameter estimate changes were seen – suggesting

gender, age and number of teeth were not significant in affecting outcome of periodontal treatment (Table 3-3).

Periodontal inflamed surface area (PISA) has been suggested to correlate with other measures of periodontal disease severity. (Park *et al.*, 2017, Nesse *et al.*, 2008, Leira *et al.*, 2018). For example, Leira *et al* showed PISA was lowest in periodontal healthy individuals at values of 34.30 ± 16.48 mm^2 and highest in cases of severe periodontitis (as per Centres for Disease Control and Prevention and American Academy of Periodontology classification of periodontitis cases (Page and Eke, 2007)) with values of 2309.42 ± 587.69 mm^2. Patients in the current study (across all treatment groups) had a median (Q1, Q3) PISA level of 1087.91 mm^2 (561.99, 1899.20). This value is perhaps rather low, however, would still be classified as 'severe periodontitis', according to Leira 2018 as 'severe periodontitis' was found to include a range of values from 934.71 mm^2 to 3274.96 mm^2. This finding may be due to patients in this study having received basic periodontal care previously by their general dentist, prior to inclusion in the current analysis. Furthermore, if a site does not bleed (even if increased probing depth is present), this site will not 'count' towards the PISA calculation which will also affect the calculated PISA value. PISA however serves as a useful amalgamation of multiple clinical indicators of periodontal disease. It was demonstrated (Figure 3-1A) that all treatment approaches resulted in significant reductions in PISA ($p<0.001$) following treatment (Table 3-2).

To compare clinical parameters between treatment groups at day 90 post treatment, Univariate General Linear Models were created controlling for successively more confounding variables. Non-parametric data were commonly identified within Day 90 data sets. This finding is likely due to the previously described differential in response of single and multirooted teeth to non-surgical periodontal treatments (Suvan *et al.*, 2019, Badersten *et al.*, 1987, Hamp *et al.*, 1975), leading to a skew in the data. Models created required normally distributed data and as described, some variables in the current analysis required transformation and this is therefore a potential limitation of the study. Alternative non-parametric testing such as Friedman test (for paired data) may have been useful. It was established that improved clinical outcomes were

comparable across all treatments, regardless of clinical variable used for assessment (Table 3-3). This finding was consistently present from the unadjusted model to the fully adjusted model. However, results of statistical testing must be interpreted with caution in the current study as the RCT (hand and ultrasonic treatment groups) was powered only to detect differences in CRP at day 1.

The similar response to treatment in each treatment group (Table 3-2, Table 3-3) was expected given current knowledge of clinical equivalence between hand and ultrasonic instruments (Tunkel *et al.*, 2002, Suvan *et al.*, 2019). As expected, combination treatment also resulted in broadly similar clinical outcomes. However, a suggestion of a trend towards marginally more favourable outcomes in the combination treatment group is present in illustrated 'change' data (Table 3-2). For example, median pocket closure rate for combination was 70.42 %, compared to 53.16 % and 62.54 % for hand and ultrasonic instrumentation respectively. A similar trend is displayed in BOP, plaque and CAL values – all favouring combination treatment by a small but noticeable margin. An explanation for this finding may lie in higher baseline levels of periodontal disease in the combination group (Table 3-1) (for example – baseline PISA in the combination group = 1277.45 mm^2, compared to 1010.02 mm^2 and 957.93 mm^2 in hand and ultrasonic groups at baseline) – thus leading to a more pronounced response to treatment, as is expected in more severe cases (Cobb, 2002, Smiley *et al.*, 2015, Suvan *et al.*, 2019). Furthermore, Cobb 2002 reported with initial probing depths of 4-6mm a 1.29mm mean PPD reduction; whereas initial probing depths of >7mm led to 2.16mm mean PPD reduction following non-surgical periodontal therapy. A larger study would be required to further investigate whether there is a true difference.

Good patient self-performed oral hygiene is linked to clinical outcomes. Historically it has been reported that regular professional visits are key to reducing plaque accumulation (among other markers of periodontal disease) and by extension professionally recorded plaque scores (Lertpimonchai *et al.*, 2017, Lovdal *et al.*, 1961, Axelsson and Lindhe, 1981b). The majority of this evidence is available from studies examining Supportive Periodontal Therapy. For

example, Axelsson and Lindhe's study in 1981 demonstrated superior plaque scores for patients placed on a carefully designed supportive regime, compared to a control group of patients not enrolled in such a program. Therefore, one could postulate that periodontal therapy provided over more appointments may yield superior plaque scores than treatment provided over a shorter timescale/number of appointments. In the current study, patients receiving hand or ultrasonic instrumentation did so over the course of two treatment visits, within 24 hours of each other. For comparison, subjects in the combination treatment arm received treatment over a minimum of four visits over the course of approximately two months (median number of visits = 4.5). Values of median (Q1, Q3) change (reduction) in plaque scores were 44.35 (18.10, 54.58) %, 33.23 (15.21, 48.67) % and 42.0 (27.75, 56.75) % for hand instrumentation, ultrasonic instrumentation and combination approaches respectively (Figure 3-1E). These changes, between groups, were not statistically significant (Table 3-3). Although patients in the hand and ultrasonic groups had fewer treatment visits, these patients returned to the clinic for sample collection at day 1 and day 7 post treatment, thus resulting in a similar number of 'episodes of contact' with the professional dental team as the combination group – this may help explain similar plaque score changes between groups (assuming professional contact episodes influences changes in plaque score). Nonetheless, the current study suggests fewer professional treatment visits may be equivalent to multiple visits with regards to fortifying improved plaque scores for patients undergoing non-surgical periodontal treatment.

Defining a reliable endpoint for 'success' in periodontal therapy has several notable challenges. The common practice of reporting mean PPD data and percentage of 'closed' pockets results in widely variable data, which is difficult to apply across populations with varying levels of periodontal disease. Consistently applying objective parameters of success, especially with such a complex disease as periodontitis, is undeniably challenging. Difficulties in reliability in measurement of PPD, BOP and plaque as well as clinical transferability further compound such issues. Attempts were made by a variety of authors (Badersten *et al.*, 1990, Cobb, 2002), perhaps most notably Lang and Tonetti (Lang and Tonetti, 2003), to combine multiple indices to help achieve

reliable markers of success to inform further periodontal treatment decisions in practice. Indeed, some goals of periodontal therapy may prove to be wholly unrealistic (such as achieving full mouth pocket closure or BOP <10%) and perhaps unachievable for certain periodontal patients with more advanced disease. These concepts were explored in detail in a 2020 study by Feres *et al* (Feres *et al.*, 2020). A robust attempt was made to propose a reliable single clinical end point for periodontal trials. This review analysed 4 RCTs with a total of 724 patients. Outcomes were assessed at 1 and 2 years post treatment. Conclusions were drawn which suggested ≤4 sites with PPD of ≥5 mm was 'effective in distinguishing between patients showing signs of post-treatment periodontal disease remission from those showing signs of uncontrolled disease'. Other highlighted factors of importance were BOP with >10% at 1 year being suggested as high risk for periodontal disease relapse. Another review article from 2020 (Loos and Needleman, 2020) explored clinically meaningful endpoints of periodontal therapy and reported the presences of PPD of ≥6 mm and bleeding on probing scores ≥30% as high risk for future tooth loss. This review included patient-reported outcomes, which are generally notable in their absence in the literature on periodontal treatment outcome assessment – this topic will be considered in Chapter 5 of the current work. In the current study, only 16% of study participants (10 patients) achieved Feres' criteria of ≤4 sites with PPD ≥5mm. No patients fulfilled all aspects of the Scottish Dental Clinical Effectiveness Programme's criteria for successful periodontal treatment (Scottish Dental Clinical Effectiveness Programme, 2014). The breakdown of constituent criteria would suggest expecting all sites to resolve to <4mm PPD is extremely challenging, relative to other criteria. Furthermore, findings presented in Table 3-4 would render 100% of patients in the current study as 'Currently Unstable' in the most recent classification of periodontal disease from the Joint Workshop between the American Academy of Periodontology and the European Federation of Periodontology (Papapanou *et al.*, 2018) as all patients had at least one pocket of ≥5 mm. Encouragingly, the study sample achieved 55% of patients reaching close to the mean level of pocket closure (57%) reported in a recent systematic review (Suvan *et al.*, 2019) which reported data at 3 months follow up (similar to the current study).

Interestingly, no single patient showed consistent ‘response’ or ‘non-response’ with respect to their performance across an extended range of published success criteria in periodontology. It is worth noting that some objective criteria for success (SDCEP (Programme, 2014)/Lang and Tonetti (Lang and Tonetti, 2003)) were created to be applicable following a full non-surgical and surgical course of periodontal therapy (and often including a period of supportive periodontal therapy) and not following solely non-surgical therapy (as presented in the current analysis). The results presented in Table 3-4 and Figure 4 demonstrate published criteria of periodontal outcome assessment vary widely between each other and can be applied with highly variable results to real patients within the current clinical study. No treatment group showed superiority as judged by ‘responder’ status (Table 3-4, Figure 3-4). However, combination instrumentation provided relatively high numbers of patients achieving <10% BOP (from SDCEP criteria), compared to other treatments. The explanation for this finding is not clear but may be due to more appointments to encourage oral hygiene and therefore reduce gingival bleeding. Nevertheless, this is contested by Table 3-4’s presentation of equivalence in plaque and BOP scores between treatment groups.

As is evident, very low numbers of patients achieved objective clinical success as measured by published criteria. These results further highlight the challenges in predictably achieving multiple parameters of success within clinical periodontal therapy.

The clinical results in the current study appear largely comparable between groups. However, the time taken to achieve those results was on average nearly 22 minutes faster using ultrasonic instrumentation compared with hand instruments. This equates to approximately 22% reduction in treatment time if ultrasonic instruments exclusively were used instead of hand instruments. This figure is within the region of that reported in a systematic review on the subject by Tunkel (Tunkel *et al.*, 2002) of 36.6%. Mean treatment time per tooth in the current study was 3.46 mins and 2.80 mins for hand instruments and ultrasonic instruments respectively, emphasising the time efficiency of ultrasonic instruments. This value is similar to that reported (approximately 3

minutes/tooth) in a seminal paper (Badersten *et al.*, 1981). This time saving, coupled with the previously discussed absence of difference in treatment outcomes provides a compelling argument in favour of the use of exclusively ultrasonic instruments in the treatment of periodontitis by non-surgical means. The European Federation of Periodontology have also recently acknowledged the additional time and skill required for hand instrumentation in their 2020 S3 Level Clinical Practice Guideline (Sanz *et al.*, 2020a). However, at the time of writing, aerosol generating procedures (such as the use of ultrasonic instruments) are discouraged due to potentially higher COVID-19 viral transmission risk. This factor may prove an important consideration in post-pandemic periodontal care.

Within the context of an exploratory analysis, as disease severity increases, time for hand instrumentation also increases significantly. As previously shown in Figure 3-2, mean treatment time for ultrasonic instruments was lower overall. Together with the evidence of equivalent clinical outcome in the current study (Table 3-2, Table 3-3, Figure 3-1), these findings provide further detail of the efficacy of ultrasonic instrumentation (compared to hand instrumentation) specifically in the treatment of patients with more advanced periodontal disease. This theory supports the currently held belief ultrasonic instruments are 'less operator dependant' (Breininger *et al.*, 1987, Suvan *et al.*, 2019, Newman *et al.*, 2011) in comparison to hand instruments.

Non-surgical treatment of periodontitis results in an initial 'spike' in circulating serum CRP levels approximately 24 hours following treatment (Graziani *et al.*, 2010, Graziani *et al.*, 2015, Sanz *et al.*, 2020b). In the current study the increase of Day 1 CRP was evident within RCT treatment groups (no day 1 data were available from the combination treatment group) (Figure 3-5). Interestingly, the CRP increase at Day 1 seen within the RCT data, although statistically significant (across all patients), was of substantially smaller magnitude compared with that reported in similar studies such as Graziani 2015 (Graziani *et al.*, 2015) or Tonetti 2007 (Tonetti *et al.*, 2007). Graziani *et al* reported a three-fold increase in CRP levels whereas the current study showed a mean 1.67-fold increase in CRP levels (across all treatment arms). As inclusion/exclusion criteria between these two studies are almost identical, this variation in result may be due to

differences in study populations, degree of trauma caused by treatment or sensitivity of hsCRP analysis. The mean (SD) baseline plaque score for this study was 52.18 (24.17) % (across all groups) whereas Graziani *et al*. reported 70 (26) % in their full-mouth debridement group. This difference may be due to patients in the RCT having received initial periodontal treatment with their general dentist. Also, study patients received a full-mouth supragingival scale prior to treatment (Scottish Dental Clinical Effectiveness Programme, 2014, Lang and Lindhe, 2015, Suvan *et al*., 2019) (following baseline plaque scoring), which will likely have reduced plaque scores even further prior to study treatments. Tonetti *et al* (Tonetti *et al*., 2007) reported an almost 8-fold increase in CRP Day 1 after full mouth non-surgical periodontal treatment. It is evident that there is a wide range of reported CRP increase following treatment and an argument could be made advocating further research to clarify these findings.

As post treatment CRP increase is reported to relate to periodontal treatment (Graziani *et al*., 2010) and the subsequent bacteraemia (Balejo *et al*., 2017), the influence of treatment time and its effects upon CRP level is worthy of consideration. Graziani *et al*. (Graziani *et al*., 2015) reported a higher CRP spike in their treatment group with a higher overall treatment time. It is perhaps logical to expect that a higher treatment time may result in a higher level of CRP spike following treatment. This concept was explored within the current analysis. Hand instrumentation was associated with a higher treatment time (vs ultrasonic) in the current study. At Day 1 following treatment, comparing hand instrumentation and ultrasonic instrumentation, absolute median change in CRP levels were 0.57 mg/l and 0.97 mg/l respectively, compared to baseline levels. No statistical significance was noted within GLM modelling in Table 3-6. When further additional adjustment was made for more relevant confounders, no statistical significance was found. Such testing may be heavily affected by both outlier CRP data in the RCT data set and low levels of serum CRP in the study. Importantly, the RCT study was powered to detect a 1.5mg/l difference in CRP between groups at Day 1 – a figure not manifesting in the observed Day 1 data. Ultimately, this finding (a difference of 0.4 mg/l) is extremely unlikely to be clinically significant. However, larger studies with more participants would aid in corroborating this finding.

Increase in CRP following periodontal treatment has been attributed to local trauma to soft tissues leading to a systemic bacteraemia (D'aiuto *et al.*, 2004a, Graziani *et al.*, 2010). It could be postulated that a more 'traumatic' treatment may lead to a higher level of systemic inflammation. Therefore, it may be speculated that exclusively hand instrumentation – which takes longer - may result in higher levels of CRP following treatment than exclusively ultrasonic instrumentation. Median (Q1, Q3) CRP change comparing pre (baseline) vs post treatment (day 90) were 0.06 (-0.56 – 0.48), 0.15 (-0.07, 1.29) and 0.08 (-0.72, 0.41) for hand, ultrasonic and combination instrumentation respectively. These values are evidently very low and likely clinically insignificant. At day 90 follow up, CRP levels demonstrated no statistically significant differences (p = 0.28, 95% CI -0.259 - -0.867, fully adjusted Model, Table 3-6) between the hand and ultrasonic treatment groups. This finding must be interpreted with caution due to a high number of outlier data points (as illustrated in Figure 3-5) within the CRP data. Furthermore, the statistical power of the current study is not appropriate for reliable testing of day 90 CRP data in the RCT. To put these figures into perspective, a similar study by D'Aiuto in 2004 (D'aiuto *et al.*, 2004b) followed 94 subjects in a longitudinal cohort trial investigating systemic inflammation following non-surgical periodontal treatment (using mainly ultrasonic instrumentation). D'Aiuto *et al.* reported no statistically significant change in CRP levels two months following treatment however a significant decrease was noted at six-month follow up. The current study results are therefore in agreement with D'Aiuto's study. An important caveat is the data available in the current study relates to 90 days following treatment and not a longer follow up. This time period may be considered post-immediate, as opposed to immediate. In summary, CRP change measured at 90 days following treatment were similar across treatment groups.

A further consideration is the provision of periodontal treatment using either a quadrant by quadrant approach or a full mouth in 24 hours approach together with the effect upon CRP levels and cardiovascular disease risk. These two approaches were provided in the 'combination instrumentation' and 'hand instrumentation'/'ultrasonic instrumentation' arms respectively in the current

study. A 2020 joint consensus statement by the European Federation of Periodontology and the World Heart Foundation (Sanz *et al.*, 2020b) stated for patients at risk of cardiovascular events 'irrespective of the level of CVD… non-surgical periodontal therapy should be provided, preferably in several 30 to 45 min sessions, in order to minimize a spike of acute systemic inflammation'. As previously shown, despite the 'post-immediate' follow up of 90 days, no clinically significant differences were found between treatment delivery approaches (RCT groups compared to cohort group; Table 3-6) in the current study and therefore further research is warranted to explore this finding further.

3.4 Summary of Key Findings

- Periodontal treatment provided using exclusively hand instruments, exclusively ultrasonic instruments or a combination of these methods yields a comparable outcome in clinical parameters of periodontal disease.
- Ultrasonic instrumentation takes less time to complete treatment than hand instrumentation.
- There is a lack of consistency in parameters of a successful outcome and definitions of 'responder' status across published criteria of success in periodontal treatment.
- The rise in serum CRP 24 hours following completion of full mouth debridement, is similar following hand or ultrasonic debridement. This suggests the systemic inflammatory response is similar following hand or ultrasonic debridement.
- Actual serum CRP, and change in serum CRP relative to baseline, measured at 90 days following completion of treatment, is similar between all three instrumentation approaches.

Chapter 4: Economic Implications of Different Approaches to Non-Surgical Periodontal Treatment

4.1 Introduction

Within the context of a publicly funded healthcare system such as the National Health Service, cost effectiveness of common treatments is an important consideration. Periodontal disease is known to be a highly prevalent condition, with a reported UK prevalence of 75% (Organization., 2005. Accessed September 2019. Available from https://www5.dent.niigata-u.ac.jp/~prevent/perio/contents.html) and an age-standardized global prevalence of 9.8% for the severe form of the disease (Bernabe *et al.*, 2020). Periodontitis is therefore a very common condition, for which treatment is provided under the NHS. Optimising costs for such common treatments have potential to yield significant savings over the long term and improve 'value for money'.

The following cost-minimisation analysis sought to explore the cost implications of providing periodontal treatment by full mouth debridement using either hand or ultrasonic instruments (data from RCT), or by providing treatment through a blended approach over multiple visits (data from cohort study). The analysis specifically explores treatment visit organisation, periodontal instrumentation technique, material procurement and recurring maintenance costs.

The research question '*What are the costs of providing periodontal treatment within a secondary care UK dental hospital setting - comparing single modality treatment provided using a full mouth debridement approach (assuming 2 visits in 24 hours) to combination treatment provided using a quadrant by quadrant approach?*' is addressed herein.

4.2 Results

To answer the research question of '*What are the costs of providing periodontal treatment within a secondary care UK dental hospital setting - comparing single modality treatment provided using a full mouth debridement approach (assuming 2 visits in 24 hours) to combination treatment provided using a quadrant by quadrant approach?*', data was gathered relating to procurement, processing and maintenance costs of hand and ultrasonic instruments (Table 4-1). It was assumed there was a functioning ultrasonic insert-capable dental chair already in situ in the dental clinic - such dental chairs have widely varying costs. It should also be noted portable benchtop ultrasonic units are also an option. Data involving clinician, nursing and decontamination staff salaries was unfortunately not available due to time constraints.

4.2.1 Influence of Treatment Delivery Approach

A 'quadrant by quadrant' approach (cohort study) was associated with a higher number of expenditure events, compared to a 'full mouth in 24 hours' approach (RCT data) in the current analysis (Figure 4-1) – a difference of 1.3 visits on average. This was due to a higher number of treatment visits in the quadrant by quadrant group (mean (SD) - 4.3 (1.49)) compared to the full mouth in 24 hours group (all patients had 3 treatment visits) (Table 4-1).

4.2.2 Influence of Instrumentation Technique – Procurement, Reprocessing, Sterilisation and PPE Costs

Comparing single instrumentation (RCT data) with combination instrumentation (cohort study), a higher initial expense was associated with combination instrumentation (Figure 4-1). The cost of procuring both hand and ultrasonic instruments was £724.95. This difference at the procurement stage (comparing ultrasonic to combination instrumentation) was calculated as £278.91 (Table 4-1). Furthermore, higher treatment visit number associated with combination

treatment resulted in higher sterilisation, repackaging and PPE costs for the combination group, compared to exclusively ultrasonic instruments – a mean difference of £21.64 per patient. In the case of the patient with the maximum number of visits in the combination treatment group (six treatment visits), sterilisation, repackaging and PPE costs accounted for £43.84 of expense.

Exclusively hand instrumentation was associated with increased sterilisation, repackaging and maintenance costs when compared with using exclusively ultrasonic instruments. This difference equated to a further £3.52 in sterilisation/repackaging/PPE cost per course of treatment and a yearly sharpening cost of £30.40. Ultrasonic instrumentation was shown to benefit from minimal maintenance expenses as no sharpening was required (Table 4-1).

PPE cost was the same between hand and ultrasonic instruments (Table 4-1). PPE cost compounded if using a quadrant by quadrant approach due to higher numbers of treatment visits.

Overall, the treatment modality with the lowest total expense was identified as hand instrumentation carried out using a 'full mouth in 24 hours' approach (Table 4-1). Over an extended period, this initial low cost was offset by hand instrument's higher sterilisation, repackaging and maintenance (sharpening) costs. The treatment with the highest expense was combination instrumentation performed using a quadrant by quadrant approach – a £332.38 increase, compared to hand instruments using a full mouth approach. High initial expense combined with maintenance of both hand and ultrasonic instruments led to this finding (Table 4-1). As shown in Chapter 3, hand instruments required less time for treatment (approximately 21 minutes) compared to ultrasonic instruments. Therefore, in the long term, the use of ultrasonic instruments, rather than hand instruments, may result in more efficient use of the dental surgery.

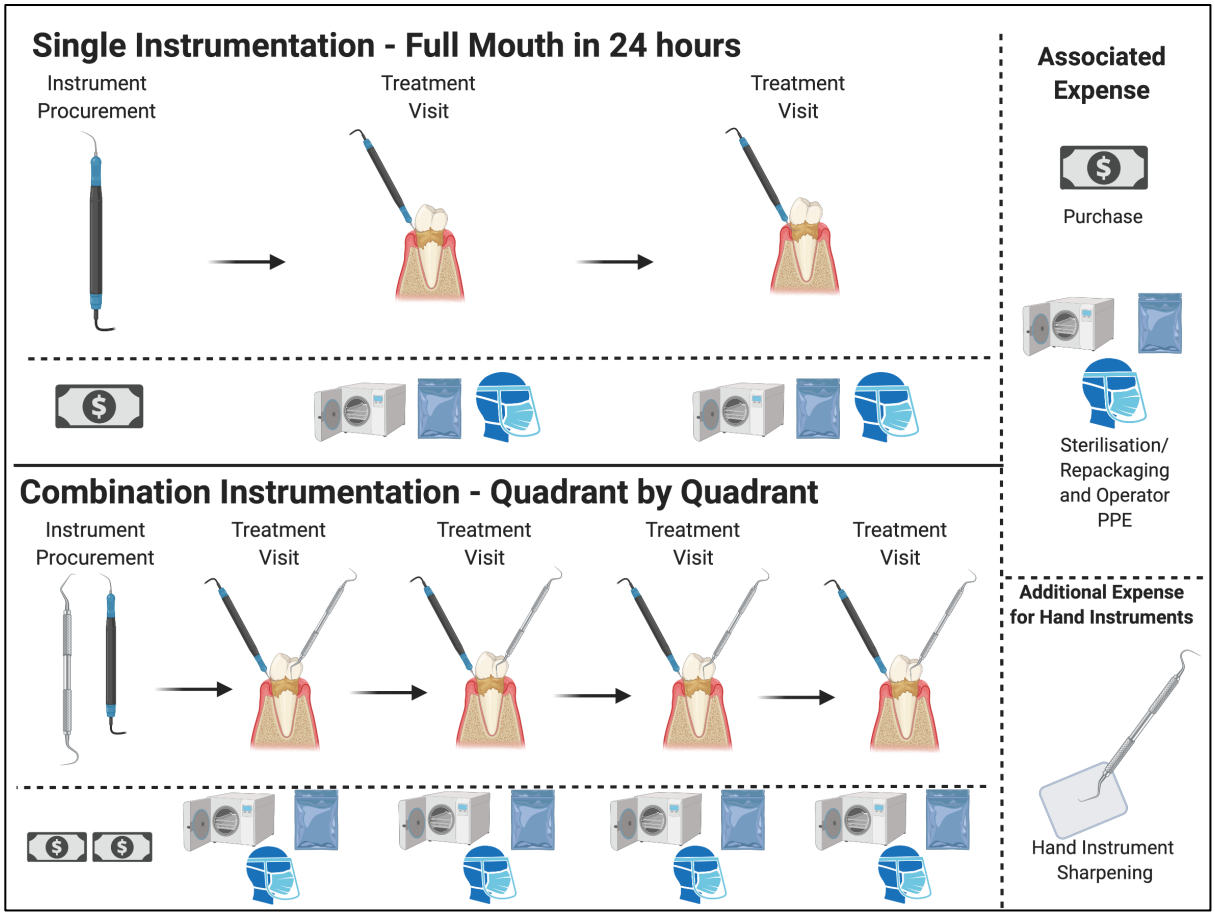

Figure 4-1 – Schematic of Costs Associated with Periodontal Treatment

Schematic of associated expense events associated with periodontal treatment within the protocols of current study interventions.

Please refer to Table 4-1 for itemised cost details

Instrumentation Technique (Delivery Approach)	Procurement	Sterilisation and Repackaging†	Maintenance (yearly)	PPE cost (per visit)	Visits*	Total Expense
Single (Ultrasonic) Instrumentation (full mouth in 24 hours)	£446.04 §	£8.76	£0 (2-minute wear check on clinic)	£0.33	3	£455.79
Single (Hand) Instrumentation (full mouth in 24 hours)	£278.89	£12.28	£30.40 (sharpening)	£0.33	3	£322.05
Combination Instrumentation (quadrant by quadrant)	£724.95	£30.40	£30.40 (sharpening of hand instruments)	£0.33	4.3	£788.17

Table 4-1 – Itemised Costs of Periodontal Instrumentation Techniques

Table of itemised costs in Pound Sterling (£) for each stage of the purchase, sterilisation and maintenance of periodontal instruments within current study protocols.

Data were gathered through liaison with NHS Procurement staff and Central Sterile Services Department managerial staff based at Glasgow Dental Hospital.

PPE cost data from https://www.dental-directory.co.uk/news/ppe-predicted-price-uplifts-post-lockdown/(accessed July 2020). This data does not account for COVID-era FFP3 masks and enhanced PPE currently used during aerosol generating procedures.

**mean number of treatment visits (including baseline supragingival ultrasonic scaling visit)*

§all inserts and barrel

†cost per full course of treatment (assuming 4 visits for combination instrumentation and 3 visits for single modality instrumentation)

4.3 Discussion

Data presented in this chapter identifies combination treatment using a quadrant by quadrant approach as the most expensive periodontal intervention studied. The overall least costly intervention, in the short term, was hand instrumentation using a full mouth in 24 hours approach – not accounting for time taken for treatment.

At the time of writing, operator PPE is a pertinent consideration, in the context of the current COVID-19 pandemic. A higher frequency of donning and doffing events is associated with treatment provided using a quadrant by quadrant approach due to a higher number of treatment visits. With the use of enhanced PPE (Cochrane, 2020) to limit transmission of the virus, higher costs are inevitable if this practice is maintained in the future. Costs could therefore be minimised by performing fewer donning/doffing procedures associated with a full mouth treatment approach. From Figure 4-1, it is evident a single instrumentation approach delivered via a full mouth in 24 hours technique has the least associated cost with least events of expenditure.

Exclusively hand instruments (full mouth treatment in 24 hours) may be significantly less costly at procurement, when compared to ultrasonic instruments (Table 4-1). However, as time passes, ultrasonic instrumentation has less maintenance requirements (no sharpening required), lower sterilisation costs and processing costs. The use of ultrasonic instruments eliminates the yearly £30.40 sharpening fee incurred by treatment involving hand instrumentation. This yearly figure is an estimate and many manufacturers recommend sharpening hand instruments following each use. Moreover, the lower sterilisation and processing cost of ultrasonic instruments yielded a £3.52 cost saving per full course of non-surgical periodontal treatment. This is due to the higher number of physical instruments in a hand instrument kit (eight hand instruments compared to five ultrasonic inserts per kit in the current study) – resulting in higher sterilisation and reprocessing expense. Currently, the COVID-19 pandemic highlights that ultrasonic use is an aerosol generating procedure

(AGP) and therefore requires additional PPE and fallow time between procedures. At this time, therefore, the data presented here could be used as a basis for cost calculations of time savings vs PPE/fallow time costs. There are likely to be ongoing changes to AGP risk mitigation strategies. For example, it could be speculated that accurate point of care testing and eventually successful vaccination and herd immunity are possible. Such changes would negate the need for additional PPE and fallow times for AGPs, and thus the current findings would again be applicable. No data exists on instrument longevity for ultrasonic instruments due to numerous variables involved – for example: tip wear, insert stack deformation, barrel coil malfunction and irrigation malfunction. Combination instrumentation treatment on a quadrant by quadrant basis was more expensive than either single instrumentation approach. This is explained by: the purchase of both instrument sets initially; more visits for treatment; more PPE expenses; both instrument sets requiring sterilisation and repackaging at each visit and also sharpening needed for hand instruments.

Aside from the cost to the NHS (Table 4-1), patient appointments also have an associated cost for the patient themselves. This cost includes lost earnings, expense of travelling to the clinic and time spent in the appointment (it is assumed the patient is travelling from and to their place of residence). Using UK based data (including treatment time data from the current study) this cost may be estimated at approximately £20.85 per appointment (calculated using average hourly UK income (£11.82 (Gov.Uk, 2020)), average distance from a UK dental surgery [mean 10.7km (England, 2018)], average public transport [UK return bus ticket- £2.33 (Tas, 2018)] costs and approximate bus speed [60km/hr]). Therefore, it is advantageous that treatment is provided over fewer appointments if possible. Not only would this practice save NHS money (Figure 4-1, Table 4-1) but patient expenses are also minimised.

Costings discussed within this chapter were gained from a local NHS material acquisition portal and thus may vary significantly according to health board and general dental practice. This may adversely affect the external validity of the findings. Monetary values presented serve as an indication of potential costings, not an absolute representation. No consideration was given to the purchase cost

of an ultrasonic base unit itself – these units are associated with significant cost implications and would potentially affect results further in favour of hand instruments. This factor was discounted as ultrasonic base units were readily available within the NHS Dental Hospital environment studied. Such dental chairs can cost in the region of £2499.99 (DentalPlaza®) to £3562.55 (Quirumed®) and beyond. Benchtop 'portable' ultrasonic machines have a cost of approximately £400 but may reach costs of up to £1600 (Cavitron® Jet Plus), subject to manufacturer and features. With regard to time efficiency of treatment and its associated costs, a UK based private dental hygienist hourly rate has been reported between £27/hour and £32/hour (based on data from 1,216 salaries (Neuvoo.Co.Uk, 2020)). It is therefore not an insignificant saving for an employer to recommend the use of exclusively ultrasonic instruments – given this study's findings of faster treatment and similar clinical outcomes (Chapter 3). In the UK NHS general dental practice setting, the 'break even' hourly rate for NHS dentistry has been reported as £93/hour (Council, 2003). The utilisation of 'full mouth in 24 hours' treatment and single modality treatment therefore would improve practitioner's likelihood of achieving this challenging target.

Challenges exist in applying standard economic health measures to dentistry and, in particular, periodontology. A measure such as the Disability Adjusted Life Year (DALY) was created by the World Health Organisation, accounts for mortality and nonfatal health consequences and is often used as a denominator in cost-effectiveness ratios (Salomon, 2014) for healthcare interventions. However, its application to periodontology is challenging as the 'disability' caused by periodontal disease often manifests as compromises in stress levels (Marcenes and Sheiham, 1992) and quality of life (Ferreira *et al.*, 2017, Needleman *et al.*, 2004) for the patient which are notoriously difficult to quantify in monetary terms. Emerging evidence of a correlation between improvements in quality of life and patient's willingness to pay for an intervention (Lachaine *et al.*, 2003) may yield promise in quantifying improvements in QoL in monetary terms. However, there exists a need for further research into this field to aid future periodontal intervention economic analyses.

4.4 Summary of Key Findings

- Periodontal treatment provided using a single instrumentation approach is less costly than using a combined instrumentation approach.
- Periodontal treatment delivered by a ‘full mouth in 24 hours’ approach was associated with fewer episodes of expenditure, compared to a ‘quadrant by quadrant’ approach.
- Ultrasonic instrumentation was associated with the highest initial procurement cost however had the lowest maintenance and processing costs, and was associated with faster treatment time, which may further offset higher initial purchase costs.

Chapter 5: Patient Perspectives of Periodontal Treatment “Study 1”

5.1 Introduction

Quality in healthcare is multifaceted, described as involving multiple concepts including ‘effectiveness’, ‘efficiency’, ‘equitable’, ‘safety’, ‘timeliness’ and ‘patient-centredness’. Furthermore, driving up quality, is one of the core values of the ‘Mission Statement’ for NHS Scotland (Communications, 2020). Within the last 10 years, particular emphasis has been placed on patient reported outcomes as a measure to assess quality in healthcare (Baiju *et al.*, 2017). Furthermore, a patient centred approach comprises treatments regarded as valuable and effective by patients themselves. The benefits of periodontal treatment from a clinical perspective have been explored both within this study and in the wider literature (Suvan *et al.*, 2019). However, reports of patient experience specifically following periodontal therapy are an area requiring further research and indeed may be key in the development of meaningful endpoints of periodontal treatment (Loos and Needleman, 2020).

This chapter aims to capture and discuss patient reported outcomes associated with different periodontal instrumentation techniques and address the research question ‘*What were patient experiences of receiving periodontal treatment?*’.

5.2 Results

5.2.1 Patient Reported Outcomes – Frequencies

Patient reported outcomes were analysed within the RCT Study only. Patients ("Study 1") in both RCT treatment groups found treatment effective, of educational value and had many positive comments, particularly relating to clinical staff (Table 5-1). Comments relating to positive results from treatment started to emerge from Day 7 and were most common at Day 90 in both groups. Two patients commented on the benefits of undergoing all treatment in a single day (Table 5-1).

High numbers of comments reporting 'no/nothing' (Table 5-2) when asked to suggest improvements to the treatment were documented. This implies, although does not confirm, patient satisfaction with study interventions. Of a potential 38 patients, 30 patients commented at day 90 they had no suggestions for improvements – the most frequent comment in the current analysis.

Issues raised included those unrelated to study interventions such as parking and travel (6 comments across all timepoints, both groups). The addition of a distraction in the form of background music was noted, particularly for the hand instrumentation group (6 comments across all time points) (Table 5-2, Figure 5-3). A single comment of 'grinding noise of scaler' was submitted in the hand instrument group at day 90. There were no such comments along the theme of noise in the ultrasonic group at any time point (Table 5-2).

Responses were collected at day 1, day 7 and day 90. Patient responses were broken down into themes, timepoints collated and only individual patient's overall comment counted, thus excluding repeated duplicate responses by the same patient. These data demonstrated approximately equal numbers of patients in both treatment groups commenting on the positive experiences from treatment and also positive results from treatment. For example, seven patients (37%) in the hand instrumentation group commented on positive experiences of

treatment; where eight patients (44%) in the ultrasonic instrumentation group provided such comments. Patients in both groups had similar concerns over accessibility of the dental clinic (Table 5-3). No patients in the ultrasonic instrumentation group communicated issues with the noise generated during treatment; whereas three unique patients reported this issue in the hand instrumentation group (Table 5-3). Difficulties accessing the clinic were reported by both hand instrumentation and ultrasonic instrumentation treatment groups at two and three patients respectively.

	Hand Instrumentation (n=19)			Ultrasonic Instrumentation (n=18)		
	Day 1	Day 7	Day 90	Day 1	Day 7	Day 90
'Amazing'	1	-	4	1	1	1
'Pain Free'	6	3	-	3	1	3
'Comfortable'	1	-	-	3	-	-
'Friendly/caring Staff'	1	3	1	3	-	7
'Positive experience'	3	-	1	1	2	-
'Well informed'	2	1	-	1	1	-
'Educational'	3	3	10	2	3	1
'Straightforward'	2	-	-	1	-	-
'Thorough'	1	1	3	2	2	-
'Very pleasant'	1	1	-	-	-	-
'Professional'	1	2	2	3	-	-
'Put at ease'	1	1	3	-	1	-
'Good'	-	1	-	1	4	2
'Fantastic'	3	3	1	2	1	1
'Relaxing'	1	-	-	3	2	1
'Better than expected'	2	-	-	3	-	-
'Happy treatment completed in one day'	-	2	-	-	-	-
'See the difference'	-	1	2	-	3	-
'No bleeding'	-	2	3	-	-	-
'Great result	-	-	5	-	-	6
'Mouth feels cleaner'	-	-	3	-	-	2
'No sore gums'	-	-	2	-	-	-
'Improved confidence'	2	-	-	-	-	2

Table 5-1 - Patient reported outcomes following periodontal treatment – Question 1

Frequency table of patient reported outcomes to a question asked to patients following treatment using hand or ultrasonic instruments: 'Thinking about the treatment in your own words, can you describe the experience of treatment?' Responses were analysed and categorised into themes and tabulated.
Please note no data was available for combination treatment and some comments are repeated by the same patient across time points.

	Hand Instrumentation (n=19)			Ultrasonic Instrumentation (n=18)		
	Day 1	Day 7	Day 90	Day 1	Day 7	Day 90
'No/Nothing'	13	13	14	15	11	16
'Don't think so'	1	1	-	1	-	-
'Difficult to access clinic'	1	1	-	1	-	-
'Honestly no'	1	-	-	-	-	-
'Difficulty parking'	-	-	-	-	2	-
'Not sure'	-	-	-	-	2	-
'Travel'	1	1	2	-	-	-
'Addition of background music'	2	2	2	-	-	2
'Appointment reminders'	-	-	-	-	-	1
'Cup of tea'	-	2	-	-	-	-
'Grinding noise of scaler'	-	-	1	-	-	-

Table 5-2 – Patient reported outcomes following periodontal treatment – Question 2

Frequency table of patient reported outcomes to a question asked to patients following treatment using hand or ultrasonic instruments: 'Is there anything that would have made it a better experience?'

Responses were analysed and categorised into higher level themes and tabulated.

Please note no data was available for combination treatment and some comments are repeated by the same patient across time points.

Theme of Comment	Hand Instrumentation (n=19)	Ultrasonic Instrumentation (n=18)
Positive Experience of Treatment	7 (37%)	8 (44%)
Positive Results of Treatment	5 (26%)	6 (33%)
Clinic Accessibility Difficulties	2 (11%)	3 (17%)
Noise of Treatment	3 (16%)	0

Table 5-3 – Patient responses to Question 1 and Question 2 – High Level Themes

Frequency table of patient reported outcomes to questions asked to patients following treatment using hand or ultrasonic instruments.

Unique patients responding within themes are shown, across all time points combined. Some patients are counted across multiple comments.

5.2.2 Patient Reported Outcomes – Visualisation of patient response

Appreciation of trends in data was gained by the creation of word clouds, a content analytic technique based on frequency of occurrence. Word clouds were utilised due to their simplicity in communicating the focus of a group of qualitative, free-text data (Atenstaedt, 2012). This technique has been demonstrated to improve comprehensibility of data, particularly for individuals not familiar with numerical tables or statistical analysis methods (Bletzer, 2015).

Overall, comments had very similar themes between groups. Common themes included pain free treatment, thorough treatment, praising of staff manner and satisfaction at results from treatment (Figure 5-1, Figure 5-2). These themes were alike, often with the same vocabulary, across treatment groups.

Similarly, responses to the question asking for suggestions for improvements to study protocols were comparable between treatment groups, with the trend emerging of more numerous comments regarding noise generated during treatment within the hand instrumentation group. Some patients in the hand instrument group also mentioned the desire for a cup of tea – although this seemed to relate to recovery after providing blood samples akin to what happens in the blood transfusion service. Again, satisfaction with treatment was inferred through numerous ‘no’ responses to this question. Word clouds (Bletzer, 2015) of positive comments are densely populated (Figure 5-1). In comparison, the word clouds on potential improvements having excess empty space highlights patients’ apparent satisfaction with study interventions (Figure 5-2).

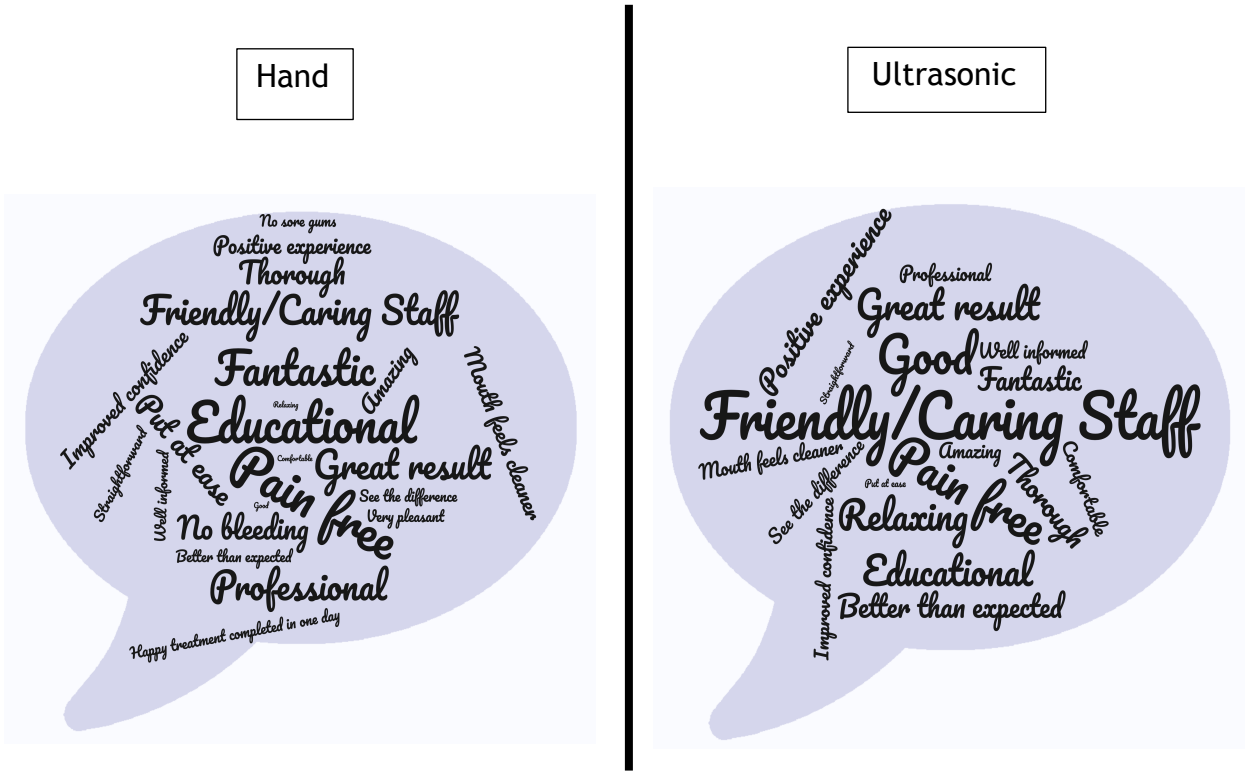

Figure 5-1 – Word clouds of patient reported outcomes to Question 1

Word cloud of common responses to the question posed after treatment:
'Thinking about the treatment in your own words, can you describe the experience of treatment?'

Responses were analysed and categorised into themes.

Day 1, Day 7 and Day 90 responses were pooled, and separate word clouds created for hand instrumentation and ultrasonic instrumentation groups.

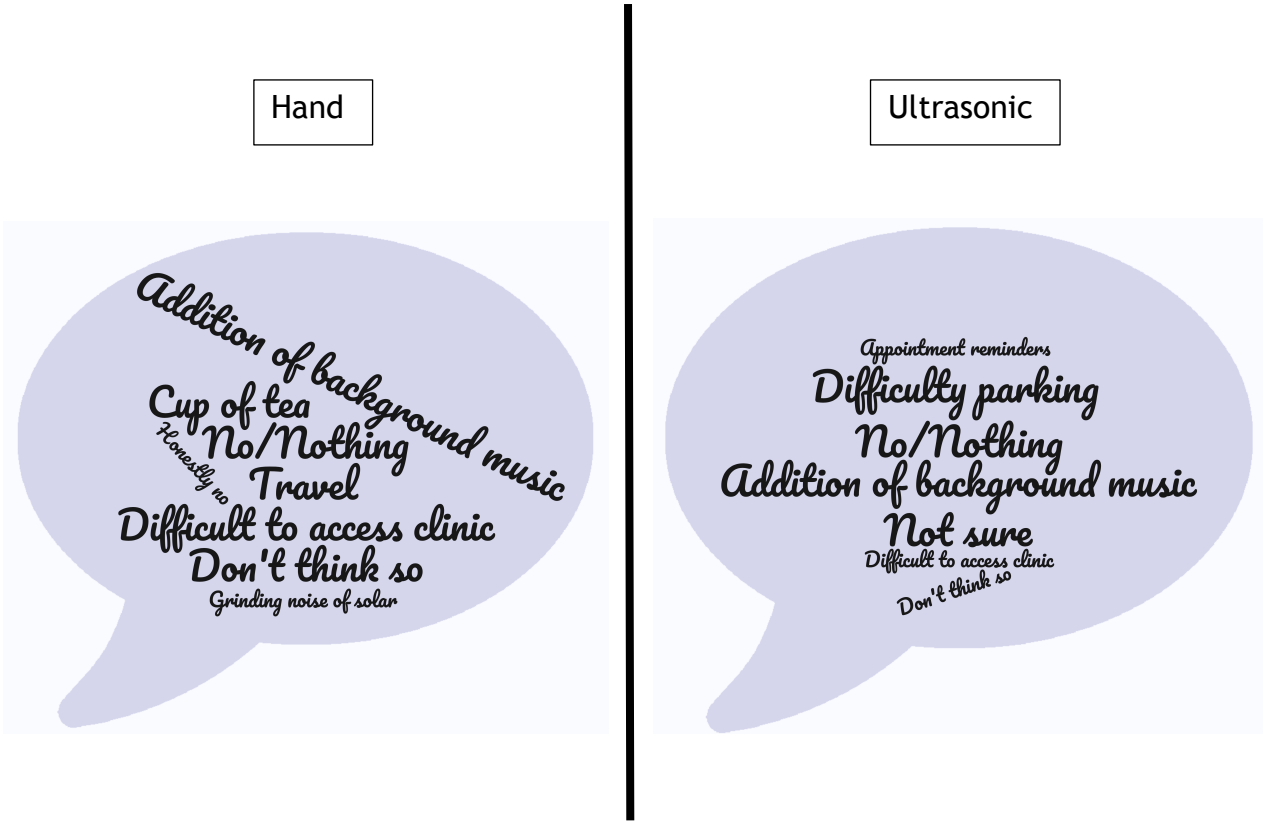

Figure 5-2 – Word clouds of patient reported outcomes to Question 2

Word cloud of common responses to the question posed after treatment:
'Is there anything that would have made it a better experience?'
Responses were analysed and categorised into themes.

5.3 Discussion

Data in the current chapter explored patient-centred reported outcomes following periodontal treatment by one of two instrumentation techniques. Key findings included high levels of patient satisfaction and comments relating to positive results from treatment.

As with all healthcare, modern periodontal treatment should strive to be as patient centred as possible. A systemic review (Buset *et al.*, 2016), following assessment of 37 eligible studies, found evidence of an association between periodontal disease and negative effects upon oral health related quality of life (OHRQoL (Sischo, 2011))– a form of patient reported outcome. OHRQoL is a multidimensional framework used to aid assessment of the impact oral conditions and treatments have upon various facets of a patient's quality of life. Examples of fields included are: 'function', 'satisfaction', 'pain' and 'bleeding gums'. Information pertaining to such fields were captured within the current study data set (Table 5-1, Table 5-2). However, data was unable to be translated directly into an OHRQoL score due to limitations in free-text, open questioning in the RCT study. Across both treatment groups following the provision of periodontal care, seven comments related to comments regarding 'function'; twenty-two comments noted 'satisfaction'; sixteen comments related to 'pain' and five comments explicitly mentioned 'bleeding gums' (Table 5-1). It would therefore appear that patients in this study, without being confined to the leading questions involved in formal assessment of OHRQoL, still offer responses similar to those included in the OHRQoL assessment proper. The OHRQoL has already been validated for clinical use and endorsed by the World Health Organisation (Petersen, 2003). However, these findings may lend further evidence to its application within clinical periodontal treatment. A promising iteration of the OHRQoL may lie in the OHIP-CP tool, developed in 2017 (He *et al.*, 2017) with a specific focus on chronic periodontitis. Validation of this tool appears very promising, with a reported Cronbach's alpha of >0.7. However, its application in further studies is warranted to elicit repeated reliability in the clinical setting.

Assessment of patient outcomes in the RCT was a secondary outcome. Each question posed to patients had a subtly different focus. The first question 'Thinking about the treatment in your own words, can you describe the experience of treatment?' may be regarded as a question probing patient experience. On the other hand, the second question 'Is there anything that would have made it a better experience' refers to both the experience of treatment received and also encourages suggestions for improving the service provided overall. As patients were already donating extra time to provide study samples (whole blood, saliva, GCF, plaque) it was felt inappropriate to impose further time burden by the addition of a fully validated questionnaire. This parsimonious technique was felt to be the most appropriate in the context of the study. Questions were discussed with a behavioural psychologist prior to their use in the study. However, a 2015 review, considering nine questionnaires from a variety of medical settings, suggested an inverse relationship between the length of a patient feedback questionnaire and the accuracy of patient responses (Pierce *et al.*, 2015). It was accepted the results from the current open questions would not be of the same quality as those from a validated, more detailed, questionnaire. Results gained from the current study may serve to aid future studies in development of a novel periodontal outcome specific questionnaire.

A systematic review emphasised the importance of considering patient reported outcomes in the assessment of periodontal care (Baiju *et al.*, 2017). This study analysed 19 clinical studies and 2 other systematic reviews, reaching the conclusion both surgical and non-surgical periodontal treatment have significant beneficial effects upon oral health related quality of life. Furthermore, a recent publication from the European Federation of Periodontology (Loos and Needleman, 2020) recommends a greater emphasis being placed on patient reported outcomes in periodontal treatment moving forward. Special mention of 'tangible' outcomes such as 'no pain' and 'aesthetic appearance' are presented. Again, in the current analysis, patients often commented on such factors via open ended questioning following treatment (Table 5-1, Figure 5-1).

Overall, patients in this study reported satisfaction following periodontal therapy – whether provided by exclusively hand instrumentation or exclusively ultrasonic instrumentation. This is evidenced by the high numbers of comments such as ‘fantastic’, ‘positive experience’ and ‘amazing’. Interestingly, a high proportion of patients reported treatment as an ‘educational’ and ‘informative’ experience, particularly at Day 90 in the hand instrumentation group (Table 5-1). Information provided to patients between groups was consistent, however. This finding may be a reflection of the lack of opportunities for patient education within general practice NHS dentistry in the UK - one of the key findings of a 2019 survey of UK based NHS dentists (Plan, 2019).

Another trend in patient feedback was, as time went on, the positive visual results from treatment (Table 5-1, Figure 5-1). Across all patients, six comments relating to this theme emerged at Day 7. However, by Day 90, twenty-one comments made reference to noticing improvements in either appearance or sensation of the gingivae. This finding is in line with expected timelines of resolution of clinical signs of inflammation (Lang and Lindhe, 2015) and serves as an interesting confirmation of this pre-existing evidence.

As previously described, there were minimal differences in emergent themes of comments in patient comments, comparing hand instrumentation and ultrasonic instrumentation groups. Overall, patients were satisfied with treatment and often could not suggest any improvements (Table 5-2, Table 5-3). It must be noted however patients may feel they are not best placed to comment on how to improve a complex service such as periodontal care in a secondary care setting and responses may be tempered due to this. Suggestions for improvements to treatment (relevant to study interventions) commonly included a desire for the addition of background music – likely as a distraction technique. This was found in both groups however was more common in the hand instrumentation group (Table 5-2, Table 5-3, Figure 5-2). A single comment in the hand instrumentation group explicitly references the ‘grinding noise of scaler’. As displayed in Table 5-3, three separate patients made comment upon the unpleasant noise of treatment in the hand instrumentation group. This finding was not seen in the ultrasonic treatment group. Overall, the data would

suggest patients are more disturbed by the operative noise produced by hand instruments, compared to ultrasonic instruments. The reliability of this finding is improved given its reporting by multiple patients (Table 5-3). Ideally, such findings would be evaluated by a split mouth or cross over study using each instrumentation technique in turn.

In recent years, patient access to dental care has emerged as a contemporary issue in both UK based (Freeman, 1999) and American populations (Bertolami, 2011). Developments have been focused on improving access to dental care in the primary care setting – as this is where the majority of treatment (particularly periodontal care) is provided. However, access to NHS specialist level care was identified by the Royal College of Surgeons England in their 2015 'Actions for the Government to Improve Oral Health' document (England, 2015). Common barriers to accessing dental care include dental anxiety, cost of treatment, perception of need and lack of access (Freeman, 1999) – which may manifest as communication difficulties or physical inability to access the clinic. In the current study, nine comments referred to access issues (Table 5-2). These comments were offered by five patients (Table 5-3). Furthermore, five comments alluded to dental anxiety (Table 5-2). Two comments also communicated appreciation at treatment being completed within a single day – another indication access and convenience are important issues for patients. It should be noted illustration of these results (Table 5-2, Table 5-3, Figure 5-1, Figure 5-2) allows assessment of the number of times these issues are raised however provides no data on the intensity of these feelings. These findings are confirmatory that patients do indeed report concerns relating to access in the context of clinical periodontal care. Further research in this field is therefore warranted to alleviate such issues and optimise future service development – specifically within a wider population, rather than the bespoke population studied in the current analysis. Future studies could utilise more focused questioning such as 'name one thing that would improve the service you received' – a technique which may have increased the number of responses to Question 2 in the current study and enhanced results.

The brevity of the questionnaire may be regarded as a strength of the current analysis as patients were not overburdened with data collection techniques and themes were able to be readily analysed. Weaknesses of the patient-reported outcome data include lack of in-depth questioning and in responses from the same patient being counted across multiple time points. However, Table 5-3 presents data with elimination of repeated responses across the same patient at different time points in an attempt to minimise this issue.

As discussed in Chapter 3, significant challenges remain in assessing outcomes within periodontology - challenges such as: variable reliability of success criteria across individual patients/populations and difficulties in combining multiple clinical variables into a single outcome measure. The inclusion of validated patient reported outcomes within a robust model (which also includes a variety of clinically meaningful outcomes) could serve to improve our ability to assess success following periodontal treatment for our patients in a balanced way. Further study into combining the fields of patient reported outcomes and clinical periodontal outcomes in periodontal care - specifically validation of meaningful changes in such outcomes - would prove valuable. Recent developments in this area of determination of the minimal important difference in quality of life measures specific to chronic periodontitis may prove valuable in quantifying the holistic benefits of periodontitis treatment in future research (He *et al.*, 2020). The DAS28 scoring system (Leeb *et al.*, 2004), for rheumatoid arthritis, is an effective example of a holistic model in healthcare which may serve as inspiration for a similar system within periodontology. This system combines objectively swollen joint counts, patient reported outcomes, blood markers and patient discomfort to arrive at an overall score – which has proven valuable as an amalgamation of the aforementioned variables.

5.4 Summary of Key Findings

- Patients were satisfied with the experience and outcome of both hand instrumentation and ultrasonic instrumentation.
- Patients in both treatment groups commented on notable improvements in self-perceived oral health.
- The only theme emerging of a negative experience relating to treatment was unpleasant noise. This finding occurred only in the hand instrumentation group.
- Some patients in both treatment groups commented on difficulties accessing the dental hospital clinic.

Chapter 6: General Discussion and Conclusions

6.1 Discussion

This thesis, and associated publication (Johnston *et al.*, 2020) document the first randomized controlled trial to investigate the impact of different periodontal instrumentation techniques on systemic inflammation following full-mouth debridement. As expected, a significant increase in CRP was observed one day following treatment across all patients; however, the increase in CRP at day 1 did not differ following hand or ultrasonic instrumentation. The data presented here demonstrate similar clinical outcomes following periodontal instrumentation, regardless of instrumentation technique. Differences in systemic inflammation, measured at 90 days post operatively showed no clinical significance. The exploratory cost/time analysis suggests in a specialist hospital setting, full mouth debridement, using exclusively ultrasonic instruments results in a cost and time saving compared with hand or combined instrumentation. Therefore, these findings have potential to impact on delivery of specialist periodontal care in the hospital setting.

The process of combining a data set from a cohort study with a randomised controlled trial, allowed a third comparator arm (combination treatment) to become available for analysis. The technique of using a combination of hand and ultrasonic instruments as a standard practice in the context of non-surgical periodontal therapy is well reported throughout the literature (Krishna and De Stefano, 2016, Suvan, 2005, Suvan *et al.*, 2019, Cobb, 1996). The inclusion of a comparator arm was employed as a means of allowing the comparison of single modality treatment with a 'treatment as usual' arm using a combination approach. This technique has potential benefits of improving external validity and clinical application of the current study's findings. Each included study's design has its own advantages and disadvantages. Firstly, cohort studies in general are able to 'identify and evaluate cause or risk factors of diseases or health-related events' (Song and Chung, 2010) by monitoring the disease status in a group of subjects prior to and following an intervention. Benefits of cohort studies include: effective design to study rare exposures/diseases, assessment of

multiple outcomes possible and provide information of temporal relationships. In the example of the current analysis, the cohort study provided temporal data follow up following periodontal instrumentation using a combination approach. In a wider periodontology context, such a study design provides the potential to collect valuable temporal data of a variety of variables such as disease resolution, systemic inflammatory state and subgingival microbiome diversity. This data allows key analyses of changes over time. Cohort studies are not without disadvantages and may have less stringent inclusion/exclusion criteria compared to a randomised controlled trial; may be challenging in the context of rare diseases; have more opportunities for bias and are potentially subject to costly follow up regimes. The current cohort study however was generally well designed and only a subsection of patients treated were used in the current study – so as to reduce heterogeneity in the data set.

As discussed in Chapter 2, the other study included in the current analysis was a randomised controlled trial (IRAPT). Randomised controlled trials are integral to evidence based dentistry and crucially aid in the development of causal relationships (Collins and Macmahon, 2001). In the IRAPT study, aspects of design were incorporated to avoid common pitfalls (biases). Firstly, a clinically relevant research question was developed, in the PICO (patient, intervention, control/comparison, outcome) format – this is described in Chapter 2, Section 2.1. The appropriate sample size was determined by effect size estimates from a pilot study (Chapter 2, Section 2.1.5)). The sample size was designed to be appropriately large to avoid making a Type 1 error – a false positive result. Inclusion and exclusion criteria were predetermined to reduce potential effects of confounding variables (a topic explored in Chapter 3, Section 3.2.3) and subjects were as similar to one another as possible to maximise the concept of baseline matching. Subjects were then randomised to interventions via concealed allocation (in the case of IRAPT – opaque envelopes) – a technique to minimise selection bias and ensure confounders were as equally distributed as possible to each treatment group. Ideally, subjects, operators and study statisticians should be blinded throughout the course of the study – to minimise performance bias caused by differentials in investigational intervention or of exposure factors that are not related to the intervention (Schulz and Grimes,

2002). This was employed as far as possible in IRAPT however the operator was unblinded when providing treatment. The current combined analysis sought to uphold the benefits of RCT randomisation by comparing hand and ultrasonic, and then included a 3-group comparison analysis that included comparison with the blended approach. An 'ideal' trial design for comparing clinical efficacy of different instrumentation regimens is detailed below.

With regards to clinical and systemic inflammatory outcomes, the current study (being a post hoc analysis) was not specifically powered to demonstrate either equivalence, a difference or superiority between treatment groups. It should be noted the intention of this analysis was not to provide a robust analysis of clinical nor systemic inflammatory outcomes. With this in mind, the results of presented statistical analyses must be interpreted with extreme caution. However, useful data has been produced in the context of studying clinical outcomes of periodontal disease, specifically within a UK based urban population. The current analysis could be viewed as a pilot study, as it is a scaled down version of a potential subsequent study and successfully demonstrated feasibility of such a study. However, this work is ultimately a post-hoc analysis. The current analysis yielded multiple fields of data of value in future research, as will be discussed in this chapter. Data relating to effect size in changes of clinical variables that may be expected following non-surgical periodontal treatment has been gained by the current work. Put into context of discussions presented in 'Clinical Success in Periodontal Treatment' within Chapter 3, a clinically meaningful effect size may be estimated for use in sample size calculations in future research investigating the effects of periodontal treatment. Regarding designing such a study on the clinical effects of periodontal treatment, PISA has been chosen as the most appropriate single clinical outcome measurement as it provides a convenient single measure of disease state and an indication of the inflammatory status of the periodontal tissues – this may also be relevant for potential future studies investigating systemic inflammation following periodontal disease. An estimated power calculation for a hypothetical future study inspired by the work of the current study is presented in Table 6-1. As is evident, a larger sample size would be required to demonstrate equivalence of treatment groups in light of data

provided by the current study (expected effect size from treatments, mean data and standard deviation data). A similar estimation may be carried out for the measurement systemic inflammation changes following periodontal treatment (CRP level). Establishment of a clinical meaningful change in CRP level (including effects on 'hard outcomes' such as ischaemic events) following treatment remains largely unanswered (Graziani *et al.*, 2015, Graziani *et al.*, 2019, Bansal *et al.*, 2014) despite movements to alter clinical practice by a joint statement by the European Federation of Periodontology and the European Heart Foundation (Sanz *et al.*, 2020b), as discussed in Chapter 3. Therefore, the current study's results may have direct application in performing a priori power calculations in future studies aimed at investigating such a popular topic in contemporary periodontology.

<u>Research Question:</u> For patients receiving periodontal treatment, are clinical outcomes achieved by non-surgical treatment using hand instruments, ultrasonic instruments or combination instruments equivalent?			
Primary outcome measure	Differences in change in PISA following treatment (measured at 90 days following treatment)		
Study Design	3 arm randomised controlled, parallel group, **equivalence** trial		
Power and Significance levels	Alpha = 0.05 Beta = 0.2 Power = 0.80		
Observed measure of effect size (Change in PISA) from current study; median (Q1,Q3)*	Hand 936.10 (304.36, 1392.59) mm^2	Ultrasonic 743.57 (268.76, 1589.81) mm^2	Combination 1167.35 (674.53, 1743.58) mm^2
Mean and Standard Deviation of Change in PISA from current study	1057 (708) mm^2		
Approximate minimum sample size required for each group in proposed RCT[§]	54 patients per group (162 total)		

Table 6-1 – Future Ideal Study Design

Ideal future study design to assess clinical outcome equivalence between periodontal instrumentation techniques, using data produced by the current study. An estimate of required sample size with results of an approximate power calculation (Julious, 2004) is presented.

Observed differences in PISA between treatment groups in the current study were regarded **as clinically insignificant*

[§]*Difference between means of treatment groups acceptable for 'equivalence' set at 400mm^2. Patient numbers not including potential for drop out.*

The data presented throughout this thesis suggest clinical outcome comparability between all instrumentation techniques. Chapter 4 explored the financial implications to both the NHS and the patient with regards to delivering periodontal treatment through a cost minimisation analysis. The use of a 'full mouth in 24 hours' approach using a single modality (either hand or ultrasonic instrumentation) showed interesting benefits in cost effectiveness and potential for minimising number of treatment visits (Figure 4-1, Table 4-1). Chapter 5 then presented patient perspectives of periodontal therapy. It was demonstrated patients were largely satisfied with results achieved from both instrumentation techniques studied (Table 5-1). Furthermore, only patients in the hand instrumentation group reported negative comments relating to the noise of treatment (Table 5-3), an interesting finding. This was surprising as it was assumed patients may preferentially comment on the ultrasonic creating an unpleasant noise, as opposed to hand instruments – this topic would benefit from more focused research. In summary, the current analysis would suggest 'full mouth in 24 hours' treatment provided using exclusively ultrasonic instrumentation has notable benefits in reduced time for treatment, less reprocessing/sterilisation costs and similar clinical and systemic inflammatory results - compared to other instrumentation and treatment delivery approaches studied.

Some notable limitations exist within the current study. Patients included were chosen from two separate studies conducted in isolation. All patients were keen to take part in research – this may result in artificial selection of compliant patients and thus inflate study results. Results therefore may lose an element of validity for less compliant patients and a wider population. It could therefore be argued that results from the current study are more clinical efficacy data than clinical effectiveness data - clinical efficacy being defined as 'the impact of interventions under optimal 'trial' conditions' and clinical effectiveness defined as 'whether interventions have the intended or expected effect under ordinary (clinical) circumstances'(Gosall, 2015). Combining results from studies is also not ideal however attempts were made to homogenise the data set such as baseline matching by inclusion/exclusion criteria, as guided by the randomised clinical trial protocol.

By virtue of periodontal instrumentation, blinding was not possible for patients nor operators. It was assumed patients were aware of instrumentation technique received – this is due to descriptions of interventions being provided during recruitment and consent discussions for relevant studies. This could potentially lead to performance bias as patients receiving certain treatments may alter their compliance or self-performed oral hygiene if they have greater faith in a specific intervention. Observation bias may also be present due to lack of operator/examiner blinding. However, these limitations may be argued to be within all interventional periodontal research to varying degrees.

Non-statistically significant results must be treated with caution in the context of the current study. Such results may mean there is no difference in the wider population with regards to the various measures comparing hand, ultrasonic and combination instrumentation or alternatively, the sample size may not be large enough to show any differences as statistically significant. The current study was not appropriately powered to detect changes in clinical parameters, so inferring strong conclusions from such data is ill advised. Nevertheless, data serve as an interesting hypothesis creation tool for future studies. The outline of a potential ideal future study design, addressing such sample size issues, is presented (Table 6-1).

Costings discussed were gained from a local NHS material acquisition portal and thus may vary according to health board and general dental practice. No consideration was made of the salary/wages of staff involved in the processing or sharpening of relevant instruments – this may further affect the result. Monetary values presented within the current study serve as an indication of potential costings, not an absolute representation. No consideration was made regarding the purchase cost of an ultrasonic base unit itself – these units have significant cost implications and would affect results, this is discussed in Chapter 4. This factor was discounted in the current study as ultrasonic base units were readily available within the NHS Dental Hospital environment studied. The services of a health economist and the undertaking of a formal cost-effectiveness analysis would prove valuable in fully exploring cost effectiveness of periodontal therapy in further detail. Given the high prevalence of severe

periodontitis that requires specialist treatment, there is clear merit in further more rigourous cost effectiveness analysis.

Data regarding patient reported outcomes would ideally also include a form of validated scale for assessment such as the OHIP-14 scale. This has seven domains: functional limitation, physical discomfort, psychological discomfort, physical disability, psychological disability, social disability, and handicap (Slade, 1997). OHIP-14 is a shortened form of the original OHIP-49 and its reliability was demonstrated to be high (Cronbach's coefficient alpha = 0.88 (Slade, 1997)) and has been validated through assessment of associations with 'sociodemographic' and 'clinical oral status' variables and shown to reliably correlate periodontal status with quality of life (Ng and Leung, 2006). Patient reported success is another technique for assessing patient reported outcomes in periodontology however this has been demonstrated to often be contrary to findings of clinical parameters of success and thus unreliable (Liu *et al.*, 2010, Gilbert and Nuttall, 1999). Using a validated measure of patient reported outcome such as OHIP-14 would likely have led to a more robust data set and higher yield of meaningful findings in patient reported outcomes – this would have increased burden on the patients in the study.

This study benefitted from a similar number of included patients for each treatment group (compared to other studies investigating clinical outcomes in non-surgical periodontal therapy (Ioannou *et al.*, 2009, Loggner *et al.*, 2009, Quirynen *et al.*, 2006, Meulman *et al.*, 2013)), resulting in tangible outcome data for a variety of clinical, systemic and patient-centred outcome parameters. The studies from which the current study gained data (randomised controlled trial and cohort study) were both well designed, implemented and at relatively low risk of bias. This would suggest data, at least in isolation, are reliable.

The ability to compare exclusive interventions (hand or ultrasonic) to 'treatment as usual' using the comparator arm (combination) improved the current study's external validity as this third arm is likely the most relatable to both general and specialist dental practice – the environments where the majority of periodontal disease is presumably treated in the United Kingdom.

The inclusion of patient centred outcomes assists in the consideration of periodontal treatment as a holistic treatment approach. Reassuringly, results confirm the satisfaction of patients with such treatment.

Finally, this study also discussed a subject of particular interest in the contemporary periodontology literature – systemic inflammation following periodontal treatment. The results shown within the randomised clinical trial data section are of significance as results suggest equivalence of hand and ultrasonic instrumentation in provoking a systemic inflammatory response.

6.2 Conclusions

6.2.1 Clinical

- Periodontal treatment provided using exclusively hand instruments, exclusively ultrasonic instruments or a combination of these methods yields a comparable outcome in clinical parameters of periodontal disease.
- Ultrasonic instrumentation takes less time to complete treatment than hand instrumentation.

6.2.2 Systemic Inflammation

- The systemic inflammatory response to full mouth debridement, measured at 24 hours following completion of treatment, is similar following hand or ultrasonic debridement.
- The systemic inflammatory response, measured at 90 days following completion of treatment, is similar between all three instrumentation approaches.

6.2.3 Economic

- Periodontal treatment provided using a single instrumentation approach is less costly than using a combined instrumentation approach.
- Periodontal treatment delivered by a ‘full mouth in 24 hours’ approach was associated with fewer episodes of expenditure, compared to a ‘quadrant by quadrant’ approach.
- Ultrasonic instrumentation was associated with the highest initial procurement cost however had the lowest maintenance and processing costs, and was associated with faster treatment time, which may further offset initial purchase costs.

6.2.4 Patient-Reported

- Patients were satisfied with the experience and outcome of both hand instrumentation and ultrasonic instrumentation.
- Patients in both treatment groups commented on notable improvements in self-perceived oral health.
- The only theme emerging of a negative experience relating to treatment was unpleasant noise. This finding occurred only in the hand instrumentation group.
- Some patients in both treatment groups commented on difficulties in accessing the research clinic.

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Appendix I – IRAPT Participant Information Leaflet

NHS Greater Glasgow and Clyde

University of Glasgow Dental School

The Immune Response after Periodontal Treatment (Version 1.0)

Information Sheet

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information.

Who is conducting the research?
Dr Shauna Culshaw and colleagues
University of Glasgow Dental School.
Periodontics, Glasgow Dental Hospital and School, 378 Sauchiehall Street,
Glasgow G2 3JZ, Telephone 0141 211 9795.

What is the purpose of the study?
The purpose of this study is to collect blood, saliva and plaque samples, obtain Body Mass Index, and blood pressure, before periodontal treatment is started, then again 24 hours, 7 days and 90 days after treatment is finished. By analyzing these samples, we hope to understand more about how periodontal disease and periodontal treatment affects both the gums and the rest of the body.

Why have I been invited?
You have been invited to take part in this study as you have periodontal disease requiring treatment at Glasgow Dental Hospital and School.

Do I have to take part?
It is up to you to decide. Your treatment will be the same whether you choose to take part in the study or not. We will describe the study and go through this information sheet, which we will then give to you. You will be asked to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving reason. This would not affect the standard of care you receive or your future treatment.

What does taking part involve?
You will be asked to provide a blood sample, a saliva sample, a gingival crevicular fluid sample (fluid which flows over your teeth), a sample of the bacterial plaque from your gums. We will also ask to record your BMI and blood pressure. These samples and vital signs will be taken before you start periodontal treatment and again (24 hours, 7 days, and 90 days) after your treatment is completed.

Blood sample:
You will be asked to donate approximately 20 ml (4 small tubes) of blood. The blood will be obtained by trained staff, who will take blood from a vein in your arm. You may experience minor discomfort, and in a small number of people there is some bruising afterwards at the site from which the blood was taken. The bruising should disappear after a few days.
Saliva sample
You will be asked to donate some saliva by dribbling into a tube for 2-4 minutes.
Gingival crevicular fluid sample:

A very small volume of fluid (gingival crevicular fluid – GCF) normally travels from the margins of your gums across your teeth, coating your teeth with the fluid. We wish to collect this fluid by placing a small collection device on your tooth and allowing the fluid to collect. The fluid will take a few minutes to accumulate in the collection device. You should not experience any discomfort and there are no risks associated with this procedure.

Bacterial plaque sample

A small amount of dental plaque will be collected from below your gum. First, the plaque above the gum will be removed (as is routinely done during a 'scale and polish'). We wish to collect a sample of the bacteria from below the gum. The bacteria will be collected using an instrument normally used for cleaning below the gum. The bacteria will be placed in fluid so they may be stored for analysis at a later date. The removal of the bacteria from below the gum to collect the sample will be identical to removal of bacteria for normal treatment of gum disease. You should not experience any discomfort and there are no risks associated with this procedure.

Body Mass Index

Your BMI (Body Mass Index) will be taken using your height, age and weight measurements to calculate your BMI. The NHS BMI calculator will be used to carry out this measurement. A trained member of the research team will take this measurement. You should not experience any discomfort and there are no risks associated with this procedure.

Blood Pressure

A device called a sphygmomanometer will be used to measure your blood pressure. This usually consists of a stethoscope, arm cuff, pump and dial, although automatic devices that use sensors and have a digital display are also commonly used nowadays. It's best to sit down with your back supported and legs uncrossed for the test. You'll usually need to roll up your sleeves or remove any long-sleeved clothing, so the cuff can be placed around your upper arm. A trained member of the research team will take this measurement.

Patient Visits

We will carry out your periodontal treatment according to normal treatment protocols. You will attend for an initial visit to clean above the gum and at this visit we will record any areas your toothbrush is missing and give you detailed advice about how best to clean your teeth to a very high standard. We will ask to collect samples at this visit. We will provide you with an electric toothbrush and interdental cleaning aids. At the next visit, we will carry out the gum treatment. We will discuss with you how long this will take, as this will depend on the extent of your gum disease. We then ask you to return to the clinic within 24 hours so we can take samples and assess your body's response to the treatment. Seven days after the treatment we will see you to check on the healing of the gums and take samples again. Around 12 weeks after treatment, we will check your gums to see how well they have healed and take samples again. If you need any further gum treatment this will be arranged at this time.

What Will Happen To The Samples and Information I Give?

All samples will be coded and identified by your unique study number. Samples will be stored in a secure fashion in the University of Glasgow. Access to samples will be restricted to the researchers and the scientists who will ~~analyse~~ the samples. Samples will be stored in line with NHS Greater Glasgow and Clyde policies. Samples may be later transferred to laboratories both within the University of Glasgow and laboratories

who can help us with the analysis both within and out with the UK. Samples may be shared with other collaborators within the UK and outside the UK. All samples provided to collaborators will not be labeled with any personal information about you and the samples cannot be linked to you. We also seek your permission to perform further studies on these samples (in a strictly anonymous fashion) in the future for studies designed to improve care for those with periodontal disease. We do not plan any genetic testing for this study but similarly seek your permission to do this in the future (again in a strictly anonymous fashion) where it may help in studies designed to improve care for those with periodontal disease. Any further studies using these samples would only take place after further review by a Research Ethics Committee.

What are the possible benefits of taking part?
You will not receive any results from the analysis of your samples. It is hoped that by taking part in this research, you will be providing valuable information regarding the role played by the immune system in periodontal disease and after periodontal treatment and how this might affect both the mouth and the rest of the body. It is hoped that this study may help guide the development of treatments in the future for periodontal disease.

What Will Happen To The Results Of The Study?
We hope the whole study will be completed in 36 Months and be published in a medical journal thereafter. If you would like further information on the results of the study you can contact the Chief Investigator, Shauna Culshaw at the end of the study.

Who has reviewed the study?
This study has been reviewed and approved by the National Research Ethics Service.

Sponsor
NHS Greater Glasgow and Clyde

If you have any further questions?
We will give you a copy of the information sheet and signed consent form to keep. If you would like more information about the study please contact Dr Shauna Culshaw.

If you have a complaint about any aspect of the study?
If you are unhappy about any aspect of the study and wish to make a complaint, please contact the researcher in the first instance but the normal NHS complaint mechanisms are also available to you.

Thank-you for your time and co-operation.

Appendix II – IRAPT Consent Form

NHS Greater Glasgow and Clyde

University of Glasgow Dental School

The Immune Response after Periodontal Treatment (Version 1.0)
Consent Form

Patient Identification Number for this trial: _ _ _ _ _

1. I confirm that I have read and understand the information sheet for the above study.

version no	*date:*

I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily.

Initials ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. *Initials* ☐

3. I consent to allow blood, saliva, gingival crevicular fluid, and dental plaque samples to be taken for research purposes before and after my periodontal treatment.
Initials ☐

4. I consent to allow my blood pressure, pulse and BMI to be taken for research purposes before and after my periodontal treatment.

5. I agree to allow gene analysis of my tissues for research purposes *Initials* ☐

6. I agree to my anonymous samples of blood/tissues being stored and used in future research project. *Initials* ☐
I agree to my anonymous samples of blood/tissues being stored and used in future research projects, including for genetic analysis. *Initials* ☐
I agree to my anonymous samples of blood/tissue being stored and used in future research projects, in work with other researchers both within and outside the UK
Initials ☐

7. I confirm that I have received a signed copy of this information and consent form to keep. *Initials* ☐

8. I agree to take part in the above study. *Initials* ☐

Name of Patient	Signature	Date
Researcher	Signature	Date

One copy to be retained by patient, one copy to be placed in the patients' notes and one copy to be retained in study file.

Appendix III – Cohort Study Patient Information Leaflet

NHS Greater Glasgow and Clyde

University of Glasgow | Dental School

The Immune Response in Periodontal Disease (Version 1.2 6th March 2015)

Information Sheet

Non Surgical Treatment

We would like to invite you to take part in a research study. Before you decide you need to understand why the research is being done and what it would involve for you. Please take time to read the following information carefully. Talk to others about the study if you wish. Ask us if there is anything that is not clear or if you would like more information.

Who is conducting the research?

Dr Shauna Culshaw and colleagues
University of Glasgow Dental School.
Unit of Periodontics, Glasgow Dental Hospital and School, 378 Sauchiehall Street, Glasgow G2 3JZ, Telephone 0141 211 9795.

What is the purpose of the study?

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Why have I been invited?

You have been invited to take part in this study as you have periodontal disease requiring treatment at Glasgow Dental Hospital and School.

Do I have to take part?

It is up to you to decide. Your treatment will be the same whether you choose to take part in the study or not. We will describe the study and go through this information sheet, which we will then give to you. You will be asked to sign a consent form to show you have agreed to take part. You are free to withdraw at any time, without giving reason. This would not affect the standard of care you receive or your future treatment.

What does taking part involve?

You will be asked to provide a blood sample, a saliva sample, a gingival crevicular fluid sample (fluid which flows over your teeth), and a sample of the bacterial plaque from your gums. These samples will be taken before you start periodontal treatment and again when the treatment is completed.

Blood sample:

You will be asked to donate approximately 20 ml (4 small tubes) of blood. The blood will be obtained by trained staff, who will take blood from a vein in your arm. You may experience minor discomfort, and in a small number of people there is some bruising afterwards at the site from which the blood was taken. The bruising should disappear after a few days.

Saliva sample

You will be asked to donate some saliva by dribbling into a tube for 2-4 minutes.

Gingival crevicular fluid sample:

A very small volume of fluid (gingival crevicular fluid – GCF) normally travels from the margins of your gums across your teeth, coating your teeth with the fluid. We wish to collect this fluid using up to two different methods. Firstly, by placing a small collection device on your tooth and allowing the fluid to collect. The fluid will take a few minutes to

accumulate in the collection device. Secondly, or alternatively, by a few drops using sterile salt water to wash out the gum pocket and then collecting the washings using a sterile collection device. Regardless of the method of fluid collection, you should not experience any discomfort and there are no risks associated with this procedure.

Bacterial plaque sample

A small amount of dental plaque will be collected from below your gum. First, the plaque above the gum will be removed (as is routinely done during a 'scale and polish'). We wish to collect a sample of the bacteria from below the gum. The bacteria will be collected using an instrument normally used for cleaning below the gum. The bacteria will be placed in fluid so they may be stored for analysis at a later date. The removal of the bacteria from below the gum to collect the sample will be identical to removal of bacteria for normal treatment of gum disease. You should not experience any discomfort and there are no risks associated with this procedure.

What Will Happen To The Samples and Information I Give?

All samples will be coded and identified by your unique study number. Samples will be stored in a secure fashion in the University of Glasgow. Access to samples will be restricted to the researchers and the scientists who will analyse the samples. Samples will be stored in line with NHS Greater Glasgow and Clyde policies for biobanking of samples. Samples may be later transferred to laboratories both within the University of Glasgow and laboratories who can help us with the analysis both within and outwith the UK. Samples may be shared with other collaborators within the UK and outside the UK. All samples provided to collaborators will not be labelled with any personal information about you and the samples can not be linked to you. We also seek your permission to perform further studies on these samples (in a strictly anonymous fashion) in the future for studies designed to improve care for those with periodontal disease. We do not plan any genetic testing for this study but similarly seek your permission to do this in the future (again in a strictly anonymous fashion) where it may help in studies designed to improve care for those with periodontal disease. Any further studies using these samples would only take place after further review by a Research Ethics Committee.

What are the possible benefits of taking part?

You will not receive any results from the analysis of your samples. It is hoped that by taking part in this research, you will be providing valuable information regarding the role played by the immune system in periodontal disease and periodontal treatment and how this might affect both the mouth and the rest of the body. It is hoped that this study may help guide the development of new treatments in the future for periodontal disease.

What Will Happen To The Results Of The Study?

We hope the whole study will be completed in 3-5 years and be published in a medical journal thereafter. If you would like further information on the results of the study you can contact the Chief Investigator, Shauna Culshaw at the end of the study.

Who has reviewed the study?

This study has been reviewed and approved by the National Research Ethics Service Committee London – Stanmore.

If you have any further questions?

We will give you a copy of the information sheet and signed consent form to keep. If you would like more information about the study please contact Dr Shauna Culshaw.

If you have a complaint about any aspect of the study?

If you are unhappy about any aspect of the study and wish to make a complaint, please

contact the researcher in the first instance but the normal NHS complaint mechanisms are also available to you.

Thank-you for your time and co-operation.

Appendix IV – Cohort Study Patient Consent Form

NHS Greater Glasgow and Clyde

University of Glasgow | Dental School

The Immune Response in Periodontal Disease (Version 1.3 22nd November 2016)
Dr Shauna Culshaw

Consent Form – ~~Non-surgical~~ treatment

Patient Identification Number for this trial: _ _ _ _ _

1. I confirm that I have read and understand the information sheet *Insert date* Version *Insert version no* for the above study.

I have had the opportunity to consider the information, ask questions and have had these answered satisfactorily. *Initials* ☐

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason, without my medical care or legal rights being affected. *Initials* ☐

3. I consent to allow blood, saliva, gingival crevicular fluid, and dental plaque samples to be taken for research purposes before and after my periodontal treatment. *Initials* ☐

4. I agree to allow gene analysis of my tissues for research purposes *Initials* ☐

5. I agree to my anonymous samples of blood/tissues being stored and used in future research project. *Initials* ☐
I agree to my anonymous samples of blood/tissues being stored and used in future research projects, including for genetic analysis. *Initials* ☐
I agree to my anonymous samples of blood/tissue being stored and used in future research projects, in work with other researchers both within and outside the UK *Initials* ☐

6. I confirm that I have received a signed copy of this information and consent form to keep. *Initials* ☐

7. I agree to take part in the above study. *Initials* ☐

Name of Patient	Signature	Date
Researcher	Signature	Date

One copy to be retained by patient, one copy to be placed in the patients' notes and one copy to be retained in study file.