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Outcomes of Periodontal Treatment in Patients with

Rheumatoid Arthritis (OPERA):

Quantitative and Qualitative Results of a

Pilot Randomized Controlled Trial

By

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Abstract

Outcomes of Periodontal Treatment in Patients with Rheumatoid Arthritis (OPERA) was a pilot randomized controlled trial (RCT) that aimed to assess the feasibility for a larger, multi-center RCT which would investigate the efficiency of non-surgical periodontal treatment in reducing disease activity levels in patients with rheumatoid arthritis (RA).

The OPERA trial used a mixed methods approach. The quantitative approach delivered pilot data regarding the clinical outcomes of the intervention, whilst the role of qualitative data was to provide a better insight into the experiences and values of the patients that would encourage their participation in the larger, definitive study.

The findings of this trial highlighted the specific issues of the patient population, the logistic challenges and provided some possible solutions to facilitate patient participation.

Acknowledgements

Clinical research is teamwork and this PhD project would not have been possible without the fantastic people that helped me get through the 3 years journey that has led to this thesis.

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And to all my lovely patients that offered their time and effort to successfully implement the OPERA trial.

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List of abbreviations

ACPA = Anti–Citrullinated Protein Antibody

BCTU = Birmingham Clinical Trials Unit

BOP = Bleeding On Probing

CAL = Clinical Attachment Loss

CPD = Cumulative Probing Depth

DAS28 = Disease Activity Score for 28 joints

EULAR = European League Against Rheumatism

ESR = Erythrocyte Sedimentation Rate

EQ-5D = Health Related Quality of Life standardized questionnaire

GCF = Gingival Crevicular Fluid

ICF = Informed Consent Form

IL-1 and IL-6 = Interleukin 1 and Interleukin 6

IQR = Interquartile Range

OHIP-14 = Oral Health Impact Profile standardized questionnaire

PAD = Peptidyl Arginine Deiminase

PHQ-9 = Patient Health Questionnaire

PIS = Patient Information Sheet

PISA = Periodontal Inflamed Surface Area

PPD = Pocket Probing Depth

RA = Rheumatoid Arthritis

RF = Rheumatoid Factor

SD = Standard Deviation

TNF-alpha = Tumor Necrosis Factor Alpha

VAS = Visual Analogue Scale

1 Introduction

1.1 Outcomes of Periodontal Treatment in Patients with Rheumatoid Arthritis – The OPERA Study:

Rheumatoid arthritis (RA) is chronic progressive immune-mediated inflammatory condition, characterized by inflammation of the joints. Untreated, it can lead to joint destruction and consequently functional impairment and disability. Rheumatoid arthritis is associated with significant morbidity and patients with RA have a higher risk for cardiovascular conditions, which leads to increased mortality associated with RA. Over 500,000 people in England suffer from rheumatoid arthritis, with approximately 26,000 new cases being diagnosed every year [1, 2]. RA is considered to be one of the main reasons for loss of productivity and early retirement in the working population and it represents an economic burden of almost £8 billion per year [52].

Chronic periodontitis is one of the most prevalent chronic inflammatory conditions in humans. It affects nearly half of the UK adult population and over 60% of the elderly [3, 4]. Several lines of evidence indicate that periodontitis may be a causal risk factor for rheumatoid arthritis [5-7].

Given the high prevalence of chronic periodontitis in the UK, this condition may represent an important modifiable risk factor leading to increased incidence and severity of rheumatoid arthritis. Data from a few interventional studies with small sample sizes suggests some beneficial effect of periodontal treatment on the disease parameters of rheumatoid arthritis [8, 9].

The main hypothesis that guided the design of the OPERA study was that the control of periodontal inflammation by means of intensive non-surgical therapy administered by a dental hygienist would provide epistemically possible benefit in terms of reduction of rheumatoid disease activity whilst improving articular function and quality of life.

In order to be able to evaluate this hypothesis in a definitive trial, the present pilot trial randomly allocated patients with RA who also suffered from moderate to severe chronic periodontitis to two treatment arms: Immediate treatment and Delayed Treatment. The Immediate treatment group received intensive non-surgical periodontal treatment. The Delayed treatment group received oral hygiene instructions for the duration of the trial, and full treatment at the end of the study.

The patients were followed up for six months.

The primary objective of this pilot trial was to assess the feasibility of the research design and the clinical intervention, to establish recruitment and retention rates and to gauge the acceptability of the intervention and study procedures to patients through the use of mixed methods (quantitative and qualitative).

The secondary objective of this study was to collect pilot data about the efficacy of periodontal treatment in patients with rheumatoid arthritis and subsequently it's influence on health related quality of life.

1.2 Historical background

The evidence of mankind's preoccupations for oral health is lost in the mists of time. Early prehistoric populations developed basic tools and instruments to make their life easier. One of the first tools ever made was designed to remove food particles from the interdental space and alleviate pain caused by the inflammation of the gums and teeth [10]. Archeologists studied the bone loss levels on the jaws of ancient human populations all around the world, from Egypt to China from over 5.000 years ago and identified evidence of horizontal alveolar bone recession due to periodontitis [11].

It is believed that Hippocrates was one of the first ones to describe the associations between periodontitis and rheumatoid arthritis [12]. Although this might seem anecdotal since the two conditions were defined only much later, it appears that The Father of Medicine presented the case of a patient with chronic inflammation of the joints that started to feel better after having a tooth extracted.

Rheumatoid arthritis was described much later, in the XIX-th century. The first to describe this condition in a scientifically systematic way was Dr Augustin Jacob Landré-Beauvais, presenting it as a chronic inflammatory condition of the joints that is different from gout and affects mainly female patients [13]

1.3 Focal infection theory

Focal infection theory was first developed at the end of the XIX-th century together with the developments in the field of bacteriology. A large amount of studies were

showing an association between systemic conditions and oral bacteria [14]. The scientific community however, dismissed these theories later, in the middle of the XX-th century [15]. There is an increasing amount of evidence to support of a refreshed version of the "Focal infection theory" and of the role that chronic oral infections could play over the increase of systemic inflammatory burden. This role has been demonstrated especially with the recent developments in the field of periodontal medicine [14]

1.4 Oral vs systemic conditions

Periodontal disease (PD) and rheumatoid arthritis (RA) share a number of similarities at different levels. According to some authors, periodontitis and rheumatoid arthritis are so similar disorders that they are in fact the same disease with localized inflammation in different parts of the body [16]. The arguments for this are that both conditions are autoimmune, genetically modulated, causing a progressive degeneration of the cartilage tissues and bone [17, 18].

The periodontal tissue and the synovial joints share histological and morpho-anatomical similarities. The gomphosis, as component of the periodontal tissue, is a specialized fibrous joint, considered a synarthrosis and connects the tooth to the maxillary or mandibular alveolar bone. The periodontal tissue contains collagen, proteoglycans and hyaluronic acid, components that can be identified in some of the joints as well [19].

Figure 1 presents an overview of the number of scientific articles exploring the associations between periodontal and systemic conditions published every year between 2000 and 2015. This was based on a simple search performed on the Web of Science Database on the 15th of August 2016. Figure 2 presents the number of citations for all these publications.

It can be easily observed the increasing interest of the scientific community regarding the associations between periodontal and oral health.

With a constantly increasing number of scientific publications exploring the associations between oral health conditions and systemic health, we can only wonder the same question that was asked by Vieira et al in 2009 - Could the mouth finally return to the body? [20]

Published items in each year

Citations in each year
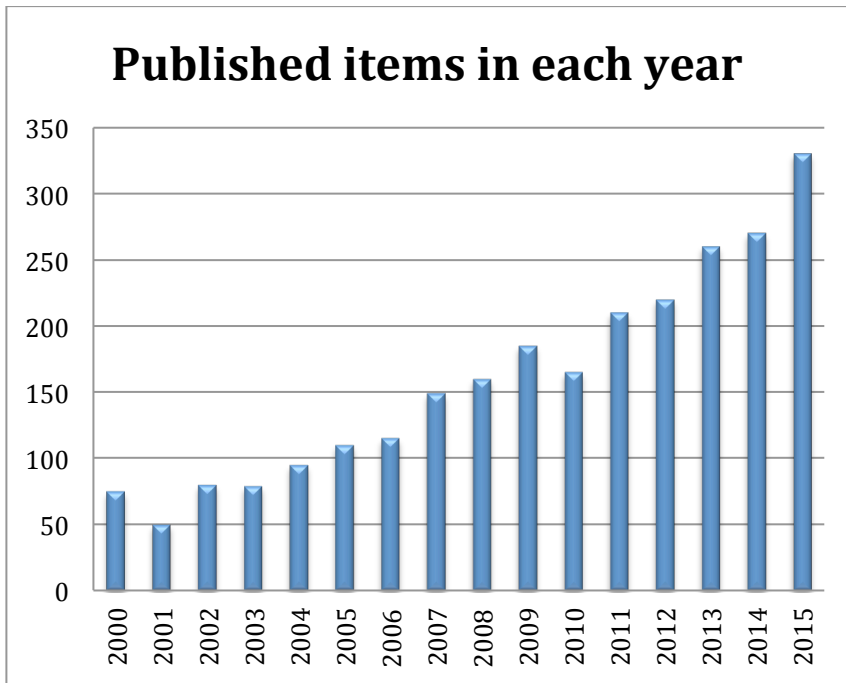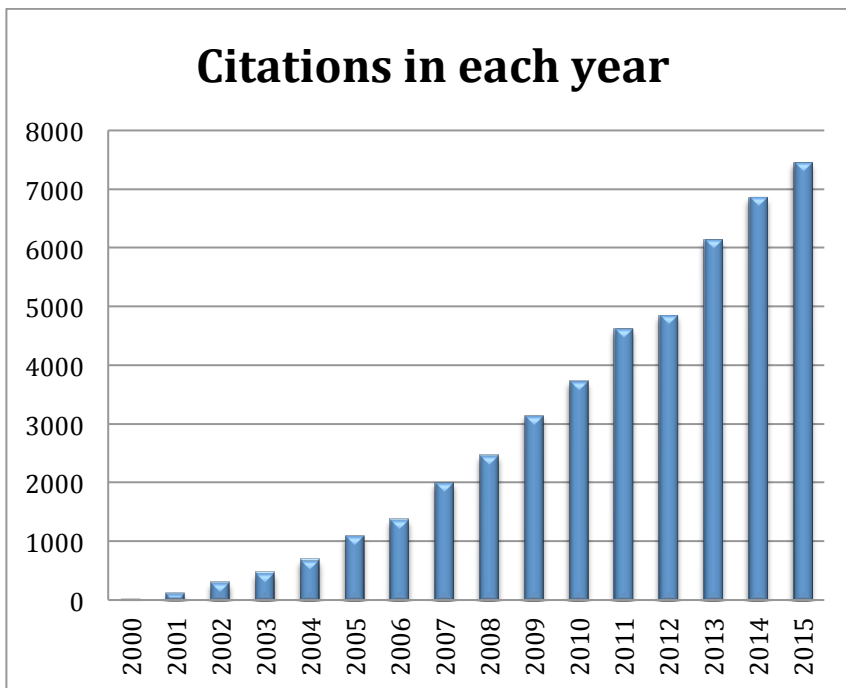
1.5 Chronic periodontitis

Periodontitis is a chronic, inflammatory condition manifested through gingival inflammation with loss of periodontal ligament from the cementum and the junctional epithelium [21]. The inflammatory process is determined by the presence of bacteria and the host modulated immune response. The progression of the disease leads to loss of connective tissue in the periodontal pockets and alveolar bone loss. Periodontitis is considered to be the main cause for tooth loss in the adult population [4, 22].

1.6 Case definitions and heterogeneity of the literature

One of the main challenges highlighted in the scientific literature is represented by the lack of consensus over a universally accepted definition for periodontitis in epidemiological studies [23, 24] resulting in a large level of heterogeneity between different studies about how periodontitis is defined. The reasons for this can be traced back to the different types of probes that are used, the number of sites of teeth that are being assessed for diagnosis and the different criteria for threshold for clinical attachment loss (CAL) and pocket probing depth (PPD) [23]

The main endpoints that are generally used to define periodontitis in epidemiological studies refer to periodontal probing depth (PPD), clinical attachment loss (CAL) and bleeding on probing – with different threshold classifications to categorize the severity of the condition.

1.6.1 The WHO definition

The Community Periodontal Index (CPI) score was developed by the World Health Organization (WHO) in order to facilitate comparisons between countries regarding the periodontal health of their populations [25]. The CPI Scores are representing percentage of persons by their maximal CPI score (prevalence rate) and the mean number of sextants with certain CPI scores: Score 0 = healthy periodontal conditions; Score 1 = gingival bleeding; Score 2 = gingival bleeding and calculus; Score 3 = shallow periodontal pockets (4–5 mm); Score 4 = deep periodontal pockets ($\geq$ 6 mm); Score 9 = excluded; and Score X = not recorded or not visible. The extent of loss of attachment (CAL) is recorded for sextants using the following codes: Score 0 = LA 0–3 mm; Score 1 = LA 4–5 mm; Score 2 = LA 6–8 mm; Score 3 = LA 9–11 mm; Score 4 = LA $\geq$ 12 mm; Score X = excluded; and Score 9 = not recorded [26].

1.6.2 The EFP definition

The European Academy of Periodontology (EAP) developed the currently accepted definition for periodontal disease. In 1999 EAP merged with the European Federation of Periodontology (EFP) becoming a subcommittee within the EFP with the objective of organizing periodically scientific workshops for specialists in the field.

The 5th European Workshop of The EAP proposed a new case definition for periodontal disease in epidemiological studies. While it acknowledged the large heterogeneity of outcome measures that are used in clinical studies it emphasized on the idea of using the clinical attachment loss (CAL) as primary outcome variable [27]. Furthermore the participants at the workshop proposed that the severity of periodontitis could not be expressed only by a single outcome variable and recommended the use of other variables as well such as periodontal probing depth (PPD) and bleeding on probing (BOP) for a more accurate description of the severity of the condition.

The participants at the workshop proposed a case definition for periodontitis based on two levels:

1. CAL ≥ 3mm on ≥ 2 non-adjacent teeth

2. CAL ≥ 5mmin on ≥ 30% of teeth present

Furthermore, for the case definition for the progression of periodontal disease, the participants proposed the presence of ≥ 2 teeth with CAL ≥ 3 mm. The group also suggested that the clinical examination could be substituted in certain cases where it is not possible to record the data by the use of dental radiographies. In this case longitudinal bone loss should be ≥ 2 m on ≥ 2 teeth [27].

1.6.3 The CDC/AAP definition

The Centre for Disease Control and Prevention (CDC) from the United States in partnership with the American Academy of Periodontology (AAP) proposed a

clinical case definition for population-based surveillance of periodontitis [28]. This classification is presented in Table 1. The classification was based on National Health Surveys conducted in the US between 1960 and 2000 and the definitions provided by the AAP in 1999 with additional modifications in 2012.

Table 1 - The CDC Case Definitions for Periodontitis

Disease classification	Clinical definition of periodontitis		
	PPD		CAL
Severe [28]	≥ 1 interproximal site with PPD ≥5 mm	and	≥2 interproximal sites with CAL ≥ 4 mm (not on same tooth)
Moderate [29]	≥ 2 interproximal sites with PPD ≥ 4 mm (not on the same tooth)	and	≥2 interproximal sites with CAL ≥3 mm (not on the same tooth)
	1 site with PPD ≥5 mm	or	
Mild or no periodontitis [28]	Neither ''moderate'' nor ''severe'' periodontitis		

1.6.4 The Joint EU/USA recommendation

The joint EU/USA Periodontal Epidemiology Working Group proposed a series of recommendations to serve as potential standards for reporting chronic periodontitis prevalence and severity in epidemiologic studies [30].

The working group presented a systematic overview of the scientific literature regarding population based, epidemiological studies for periodontitis. This included an assessment of potential study designs, sample sizes with accounting for drop-outs (with reasons), assessment of periodontal measurements and recording protocols and case definitions for periodontitis.

The working group recommended the use of the case definitions developed by the Centers for Disease Control and Prevention and the American Academy of Periodontology (CDC/AAP) as standard for reporting on periodontitis for epidemiological studies. Furthermore, considering the large amount of different

clinical endpoints, in order to be able to facilitate comparisons between different studies, the working group created a list of key items together with a ranking of their importance that are recommended to be reported on in epidemiological studies.

1.6.5 Aggregate measures of periodontal inflammatory burden

The case definitions used for epidemiological studies were developed to present an accurate description of the prevalence and incidence of periodontitis at population level. These measures, however did not present an accurate evaluation of the chronic inflammatory burden, as they did not take into account variables such as the number of teeth present or the cumulative value of deep periodontal pockets. In order to provide a more precise evaluation of the periodontal inflammatory burden that could contribute to the overall systemic inflammatory burden associated with systemic conditions, a number of different aggregate measures were developed.

The periodontal inflamed surface area (PISA) was proposed in 2008 by Nesse et al [31]. This aggregate measure was developed to quantify "the surface area of bleeding pocket epithelium in square millimeters" which represents the sum of periodontal probing depths weighted by the size of the affected tooth. PISA is calculated using clinical attachment loss (CAL), periodontal pocket depth (PPD) and bleeding on probing (BOP) [31].

A different aggregate measure used in clinical studies is cumulative pocket depth (CPD). This is calculated as the sum of the deepest probing depths for each tooth that is ≥ 4 mm [32] to ensures a minimum number of teeth with deep periodontal pockets present. Both CPD and PISA attempt to estimate the surface area of the inflamed periodontium. CPD however is characterized by a more simplistic approach compared to PISA. CPD is not using tooth specific weights nor BOP, the only measure being the deepest pocket per tooth.

1.7 Epidemiology and burden of periodontal disease in Europe

It is difficult to assess the state of periodontal health at European level. There is a lack of epidemiological data that is comparable and consistent across the different EU Member States [33]. By using data from epidemiological studies employing the Community Periodontal Index (CPI) developed by the WHO, Konig et al presented an overview of the current status of periodontal health between the EU Member States. It is believed that over 50% of Europeans are suffering of some form of periodontitis, the severe form affecting over 10% of the population with the highest prevalence (70-85%) among the 60-65 years old age group [33].

The authors of this study suggest that the actual prevalence could be even higher and there is a tendency for an increased rate of incidence among all the EU Member States [33]. This can be related on the increased prevalence of diabetes as comorbidity for periodontitis, higher life expectancy and on the large number of elderly that are able to retain their teeth at advanced age as well.

1.8 Periodontal care in the NHS

Periodontal care in the NHS is currently provided under the framework of the Dental Contract from 2006 and with the modifications of 2010 issued by the Department of Health [34]. Periodontal care in this context is represented by oral hygiene instruction, scaling and root surface debridement and supportive care. According to the Clinical Audit Committee of the Royal College of Surgeons of England periodontal diseases can be classified into 3 codes of complexity [35]. These codes are based upon the Basic Periodontal Examination (BPE) Criteria and are as follows:

Complexity 1:

- BPE Score 1 – 3 in any sextant

Complexity 2:

- BPE Score of 4 in any sextant
- Surgery involving the periodontal tissues

Complexity 3:

- Surgical procedures associated with osseointegrated implants
- Surgical procedures associated with osseointegrated implants
- Surgical procedures involving periodontal tissue augmentation and/or bone removal
- BPE Score of 4 in any sextant including one or more of the following factors:
  - o Patients < 35 years old and smoking > 10 cigarettes/day

o Concurrent medical factor affecting periodontal tissues

o Root morphology adversely affecting prognosis

o Rapid periodontal breakdown > 2 mm clinical attachment loss (CAL) in any one year

Under these guidelines, general dental practitioners are advised to only refer patients with relatively rare aggressive forms of periodontitis to specialist care. However, chronic periodontitis is under-diagnosed and under-treated in the general dental services (GDS), for a variety of reasons including the limited availability of dental hygienists in NHS general dental practices [36]. Furthermore, specialist care is more intensive than that performed within the GDS [36] and the greater time spent and expertise employed within specialist environments results in greater periodontal stability [37].

1.9 Dysbiosis and host-mediated tissue damage

Oral bacteria was first described by Antonie van Leeuwenhoek in 1683 [38, 39]. Since then, our understanding of the role played by bacteria in the mechanisms that leads to disease shifted from the idea that bacteria are the sole etiological agents responsible for diseases to the idea of bacterial homeostasis where bacteria are necessary companions for a healthy human life and humans are rather superorganisms composed of human and bacterial cells [39]. When the balance of symbiotic bacteria shifts towards parasitic bacteria or the numbers of

symbiotic bacterial organisms exceeds the number that is beneficial for the body or with other words the homeostasis is disrupted – is the moment when disease occurs [40].

In 1972, the microbiologist Thomas Luckey estimated the bacterial cells ratio to human cells is 10 to 1 in a healthy organism [41]. Until very recently, this was accepted both in science and popular culture. Later on, the National Institutes of Health from the United States published the Human Microbiome Project (HMP) which presented a comprehensive mapping of the different types of bacterial colonies in the human body [42]. Sender revised Luckey's estimate in 2016 [43] and proposed a ratio of 1.3 to 1 of microbial to human cells. [38]

1.10 Human impact (DALY, QUALY, Economic burden, QoL, mortality)

Non-communicable diseases are becoming a high priority for stakeholders and decision makers. This is a result of an increasing ageing population in most of the industrialized countries due to higher life expectancy and lower birth rates. According to a study published by Harvard School of Public Health and the World Economic Forum [44, 45] non-communicable diseases (NCDs) will cost global economies $47 trillion by 2030. Such NCDs are the leading cause of death in the UK – from the total deaths in 2008 in the UK (518 400), 23.75% were among the under the age of 70.

Economically oral diseases represent a major impact in most countries, being the fourth most expensive diseases; they represent 6-12% of the health budgets for

OECD countries and affect more than 90% of the world's population [46]. According to the British Dental Health Foundation more than 415,000 employees took days off work in 2011 due to dental problems while more than 1.1 million people took days off to look after a child suffering from oral health problems leading to yearly loss of £36.6 million for the British economy.

1.11 Epidemiology and burden of rheumatoid arthritis

The European League Against Rheumatism (EULAR) defines rheumatoid arthritis (RA) as a "chronic inflammatory disease characterized by joint swelling, joint tenderness, and destruction of synovial joints, leading to severe disability and premature mortality"[47]. The first symptoms of RA are noticed usually between the age of 35 and 50. Within 5 years of diagnosis, 40% of patients from developed countries will reduce their working week from full time to part time, with a decrease of 50% at 10 years from the first diagnosis [48]. In the UK, according to the National Rheumatoid Arthritis Society, 29.3% of the RA patients left their job with 28.4% doing so on the first year of diagnosis, and 59% within six years. With 690,000 RA patients in the UK, the economic burden represented by this condition is almost £8 billion per year and it is considered to be one of the main reasons for loss of productivity and early retirement in the working population[49] .

A recent study from Australia showed that 65% patients with RA declared that their condition affected their personal and professional relationships, the negative consequences of the disease affects especially younger people (p=0.021). Patients

reported reduced opportunity for social interaction, reduced opportunity for sports and outdoor activities as well as maintaining their roles in family life. Rheumatoid arthritis is transforming the daily routine of the patients and influences their quality of life. They have to abandon their work in certain cases, move house, accept help from external sources (family, friends or social workers) and increase their feeling of vulnerability which is added as a psychological burden for their condition [51].

1.12 Etiology and pathogenesis

The current evidence for the etiology of rheumatoid arthritis points towards both genetic and environmental risk factors. In terms of environmental risk factors, smoking is considered to be the most important one meanwhile genetic predisposition is accounting for over 50% of the new cases [52].

1.13 Progression

The pre-clinical phase of rheumatoid arthritis is manifested by the appearance of autoantibodies including rheumatoid factor (RF) and anti-citrullinated protein antibodies (ACPA).

The sensitivity of RF was estimated to 60-70% with a specificity of 78% whilst the ACPA sensitivity was estimated to higher values - between 69.6% and 77.5% and specificity between 87.8% and 96.4%[53]

The initiation of the preclinical phase and T cell activation is followed by chronic inflammatory phase with progressive tissue damage caused by cytokines IL–1, TNF-alpha and IL–6 [54].

1.14 Biological models to explain the associations between periodontitis and RA

There are several theories regarding the associations between rheumatoid arthritis and periodontal disease. Some studies suggested the hypothesis that bacteremia caused by periodontal pathogens could be an etiological agent for RA progression and pointed towards oral bacterial DNA in patients synovial fluid and serum that could be transported via free form of DNA [55]

Another model, with a wide support of the research community is pointing towards a host-mediated mechanism. This model supports the hypothesis of a potential causal relationship between periodontitis and RA severity and progression. This is based on the assumption that bacterial byproducts from the periodontal tissue could enter the systemic circulation and stimulate an increased immune response in certain susceptible individuals.

One of the main aetiopathological agents responsible for periodontal disease is *Porphyromonas gingivalis.* With the recent recognition of the importance of anti-citrullinated protein antibodies (ACPA) in RA and the discovery that *P. gingivalis* expresses peptidyl arginine deiminase (PAD), there is potential evidence to support a plausible pathobiologic mechanism by which periodontitis may cause or

sustain the inflammatory response in RA. At this moment *P. gingivalis* is considered to be the only bacterium from the oral cavity known to be capable of producing the PAD enzyme [17]. PAD is responsible for the post-translational citrullination of peptide antigens on arginine residues [56], and microbial PAD deiminates arginine in fibrin found in periodontal tissue [57]. For patients with periodontitis who are exposed to PAD therefore, to citrullinated antigens these might become systemic immunogens [9].

Before the first clinical manifestations of rheumatoid arthritis, the anticitrulinated protein antibodies (ACPA) are already present with elevated cytokines in the gingival crevicular fluid (GCF) [17, 56-58]. The levels of antibodies against *P. gingivalis* have been correlated with levels of ACPA in patients with RA [7]. Antibodies to citrullinated α-enolase are specific for RA [59, 60]; an immunodominant epitope in this protein that shows sequence similarity and cross-reactivity with *P. gingivalis* enolase could indicate a role for *P. gingivalis* infection in priming the autoimmune response in RA [60].

Recent studies have also demonstrated that the uncitrullinated peptides play a major role in the antibody response for periodontitis resulting in a systemic spread of citrullinated epitopes in the presymptomatic phase of RA. Autoantigens modified by citrullination through exposure to periodontal pathogens might sustain synovial inflammation in the context of untreated periodontitis [56]. Antibodies for uncitrullinated RA autoantigens precede the ACPA formation and facilitate the loss of tolerance to uncitrullinated peptides [61].

1.15 Epidemiological associations between periodontitis and RA

The biological plausibility of the associations between periodontitis and rheumatoid arthritis have been successfully demonstrated in animal models [62, 63] and observational data suggests a higher incidence of periodontitis in patients with rheumatoid arthritis [64-67] there is little known in terms of causality of this relationship.

The scientific literature presents an increasing amount of evidence from observational studies regarding the associations between periodontitis and rheumatoid arthritis (RA) [68]. The patients who are diagnosed with RA are more likely to have chronic periodontitis and have lost more teeth compared to those without RA [64, 69].

Table 2 presents an overview of observational studies that investigated the associations between clinical attachment loss and rheumatoid arthritis. This table was adapted from a systematic review performed in 2013 by Kaur et al [70].

Table 2 – Associations between periodontitis and RA in case-control studies

Studies	Sample size and CAL				Statistical significance
	RA patients		Non RA patients		
	N	CAL	N	CAL	
Joseph et al, 2013 [71]	100	2.88 ± 1.10	112	0.98 ± 1.04	p > 0.05
Garib et al, 2011 [72]	50	3.24 ± 0.65	50	2.09 ± 1.09	p < 0.001
Okada et al, 2011 [73]	80	3.0 ± 0.1	38	3.1 ±.01	p = 0.1
Vakar et al, 2010, [74]	101	3.05 ± 1.02	101	2.84 ± 0.89	No
Ishi et al, 2008 [75]	39	4.4% > 5.0 mm	22	2.8% > 5 mm	p < 0.05
Pischon et al, 2008 [76]	57	4.37 ± 1.3	52	3.40 ± 0.89	p < 0.001
Biyikoglu et al, 2006 [77]	17	2.6 ± 0.05	17	3.3 ± 1.2	p > 0.05
Bozkurt et al, 2006 [78]	17	4.92 ± 0.73	17	1.43 ± 0.7	p < 0.05
Gleissner et al, 1998 [79]	100	2.5 ± 1.8	112	1.0 ± 0.7	p < 0.0001
Kaber et al, 1997 [80]	50	2.6 ± 1.7	50	0.95 ± 0.7	p < 0.0001

Data from the third National Health and Nutrition Examination Survey (NHANES III) from the United States presented evidence to support a four times higher probability of having periodontitis for patients with RA, even after adjusting for potential confounders [64].

By using a mixed methods approach, the study combines the strengths of quantitative research with qualitative research and brings together the findings with

1.16 Brief introduction to qualitative research methodology

In this chapter the reader will be presented with a brief description of a number of different qualitative research designs that are most widely used and the justification for the use of each of these methodologies.

1.17 The nature of qualitative research

According to Creswell [81] there are four main perspectives that can shape a research design:

- Post-positivism
- Constructivism
- Advocacy
- Pragmatism

Post-positivism

This approach is also called the "scientific approach" or quantitative research. It is characterized by a deterministic approach for a temporal succession of the events of interest, whereby causes determine effects or outcomes.

Constructivism

This approach is also called interpretivism and is based on the direct interpretations of the study participants for different events or experiences. The views of the participants are combined with those of the researcher to provide a "subjective" interpretation of a broader construct.

Advocacy

This approach is somewhat connected to the constructivist approach and takes things a little further by actively engaging the researcher in advocating/representing the rights of the research subjects in order to change policy and/or legislation for their benefit. Specific issues are addressed through a concrete agenda o

Pragmatism

The pragmatic approach states that the research problem is more important the research method. The researcher is

Based on these perspectives [82] the five most important qualitative research designs can be described as:

- Narrative research
- Phenomenological Research
- Grounded theory
- Case Study Research
- Ethnographic Research

`Table 3 - The main methodologies used in qualitative research

Dimension	Narrative	Phenomenology	Grounded Theory	Ethnography	Case Study
Focus	Exploring the life of an individual	The essence of experiences about a phenomenon	Developing a theory from the data in the field	Describing and interpreting a cultural or social group	In-depth analysis of a single/multiple case(s)
Data Collection	Interviews and documentaries	Long interviews (=<10 people)	Interviews till saturation (20-30)	Observations and interviews over extended time	Documents, interviews, observations, artefacts
Data analysis	Stories, Historical content	Statements, Meanings, General description of the experience		Detailed description of an individuals life	Description of the "essence" of the experience
Product of the study				Ethnographic Research	

`Table 3 presents some of the main methodological approaches used in qualitative research.

1.17.1 Grounded theory research

Grounded theory research aims to explore the common experiences of individuals in order to develop a new theory and was chosen as the most appropriate for this research project. Grounded theory can be used in health promotion research and can be helpful in exploring socio-psychological problems as well as to identify determinants of various health behavior patterns.

Grounded theory is a research method that is characterized by a systematical collection and analysis of data [83]. This systematical approach made grounded theory very popular amongst researchers and it became widely used in research projects that included mixed methods as it can be paired in a more consistent way with quantitative methods [84]. It explains and shows depth of the researched phenomenon. Grounded theory is a creative process, which is used when there is no sufficient theory or knowledge related to the researched problem [85], and existent theories do not offer the solutions. Grounded theory allows for the identification of various phenomena and their changes over time. Grounded theory research is a good approach to study patients with chronic diseases [86].

The goal of grounded theory research is to

- Generate new hypothesis based on ideas and concepts

- Prioritize the importance of understanding the researched phenomenon from the perspectives of the subjects of the study, rather than presenting an objective and impartial "truth".

Grounded theory research presents a set of advantages:

- Ecological validity represents the context specificity of the grounded theory data, which reflects the situation from a real world setting. Although the data is context specific it can also be successfully used to extrapolate the results to different settings.

- Novelty of grounded theory – the potential for innovation and exploration of new areas by creating knowledge in previously unexplored areas or in areas that were approached differently before.

- Parsimony: a simple and straight forward way of reducing complex phenomena to easy to understand concepts by assessing the relationships between the different factors and the roles that are played over the outcome.[87]

Grounded theory is ideal to be used in mixed methods research in combination with quantitative research methods in order to gain an in depth understanding of the researched phenomenon. This is especially applicable for explorative research or new, previously less researched fields.

1.17.2 Qualitative vs. quantitative research

One of the main differences between qualitative and quantitative research methodology resides in the fact that qualitative research is significantly more

flexible than quantitative research. In general, quantitative methods are not very flexible. Using quantitative methods such as surveys and questionnaires, for example, researchers ask all the participants to provide answers to identical questions in the same order. The response categories from which participants may choose are typically "closed-ended" or fixed. The advantage of this inflexibility is that it allows for meaningful comparisons of the responses across participants and study sites. However, it requires a thorough understanding of the important questions to ask, the best way to ask them, and the range of possible responses.

1.17.2.1   Rigorousness of the qualitative versus the quantitative research methodologies

While qualitative research has a subjective perception of the reality from the perspective of the participants, quantitative methods are using an objective perception. The relation of the researcher to the research project is interactive in the qualitative paradigm and independent in the case of quantitative paradigm. Qualitative research methods are characterized by an informal and personal language meanwhile quantitative research methods are typically using a formal language with a clear set of definitions. Qualitative research methods are flexible by definition and allow the necessary freedom to be perfectly tailored and adapted to the specific context of a research project.

Table 4 presents a comparison on measures of rigorousness between qualitative and quantitative research approaches. According to Guba et al [88] the four

measures of rigorousness in qualitative research are credibility, dependability, transferability and confirmability. Each of these are corresponding to a measure of rigour in quantitative research.

Table 4 - Comparison between quantitative and qualitative research

Quantitative research	Equivalent in qualitative research
Validity	Credibility
Reliability	Dependability
Generalizability	Transferability
Objectivity	Confirmability

1.17.2.2   Credibility

Credibility is a measure of rigour to assess the trustworthiness and quality of the data that is presented. This is done from a perspective of depth or richness of data rather than from the perspective of large quantity of data.

1.17.2.3   Dependability

Dependability is similar to reliability as it refers to the repeatability and consistency of the methods that were used for the study in order to assure that the data is comparable with other, similar studies. It also involves a scientifically sound and consistent method to report on the collected data.

1.17.2.4   Transferability

Transferability in qualitative research is equivalent to some extent to generalizability in quantitative research. The quality of the research is assessed by the reader in order to establish if the findings of the study can be transferred to different contexts or not. A better level of comparability or transferability increases the level of credibility of the study.

1.17.2.5 Confirmability

As qualitative research could potentially be more vulnerable to bias if the researchers findings are not supported by the collected data, a second, independent researcher could check the quality of the data and if the data is supporting the findings of the study. If the independent researcher confirms the findings of the study, then the study is considered objective or confirmable from a qualitative perspective.

1.18 NICE Guidelines

There is a continuously increasing amount of interest of the scientific community towards the type of evidence provided by qualitative research methods. This interest has been obvious especially in terms of the guidelines developed by the National Institute for Health and Clinical Excellence (NICE). Between the years 2002 and 2007, 45 % of the guidelines developed by the NICE were based on qualitative studies as source of the evidence for these guidelines [89].

1.19 Sampling in qualitative research

Table 5 - Sampling methods in qualitative research

Type of sampling	Purpose
Maximum variation	Documents diverse variation and identifies important common patterns
Homogenous	Focuses, reduces, simplifies, facilitates group interviewing
Critical case	Permits logical generalization and maximum application of information to other cases

Theory based	Finding examples of a theoretical construct and thereby elaborate and examine it
Confirming and disconfirming cases	Elaborating initial analysis, seeking exceptions, looking for variations
Snowball or chain	Identifies cases of interest from people who know people who know what cases are information rich
Extreme or deviant cases	Learning from highly unusual manifestations of the phenomenon of interest
Typical case	Highlights what is normal or average
Intensity	Information rich cases that manifest information but not extremely
Politically important cases	Attracts desired attention or avoids attracting undesired attention
Random purposeful	Illustrates subgroups; facilitates comparison
Stratified purposeful	Adds credibility to sample when potential purposeful sample is too large
Criterion	All cases that meet some criterion: useful for quality assurance
Opportunistic	Following new leads; taking advantage of the unexpected
Combination or mixed	Triangulation, flexibility, meets multiple interests and needs
Convenience	Saves time, money and effort, but at the expense of information and credibility

Table 5 presents a list of different sampling types in qualitative research and a short description of the purpose of each one of these methods [90, 91]. In the OPERA trial a random purposeful sampling procedure was adopted until saturation was reached.

Sample size determination and sample selection in qualitative research are different than in quantitative research. Whilst in quantitative research, larger sample size increases the validity of the study in qualitative research, larger numbers are not increasing the quality of the study. The purpose of sampling in qualitative research is to make sure that the participants directly experienced the

problem of interest and they are covering all the possible dimensions and areas of interests.

As there can be a number of different characteristics of potential types of participants, events or processes to be sampled, the study design and research paradigm will lead the type of sampling that will be made.

1.19.1 Sample size

Estimates are provided based on previous studies, experience, pilot work, etc. It is important to take into account also the logistic aspects to carry out the study methodology and assure the sampling is feasible in the chosen context. These can be related to access to participants, communication and logistics, safety and data processing.

1.19.2 Saturation

Saturation is the one of the possible ways to determine sample size in qualitative research. Saturation in interviewing is defined as the stage in which the participants are not providing any more additional information to the researcher and the qualitative data starts to become repetitive. The common practice at this stage is for researchers to continue to conduct a small number of additional interviews to make sure that the saturation is real. If saturation is real and no more new information is provided by the participants the researchers can decide to stop the data collection and resume the sample size to the number of participants that provided data until that particular moment.

1.20 Strengths and weaknesses of using mixed research methodology

The outcomes that are important for clinicians are not always the most relevant for patients [92-94]. While clinicians can focus on clinical and biological parameters, quantitative or "hard endpoints" it has been demonstrated that patients sometimes are more concerned about issues regarding their quality of life. This often is translated by their ability to live with dignity and independently. Exploring the differences between patient and clinician centered outcomes is especially important for pilot studies where one of the main objectives is to try to understand the values, priorities and experiences of the patients all of which determine their choices for treatments and outcomes.

The qualitative research approach brings a substantial advantage to this study by providing an interdisciplinary and comprehensive approach to answer not only the research question but also to generate a deeper understanding of the phenomenon that is being studied. Through an integrated qualitative research designs we can provide a fusion of disciplinary knowledge with the know-how and personal experience of patients.

This approach was considered especially important because of the lack of information regarding the feasibility of the protocol of the interventional study. Considering that there is a lack of interventional studies regarding the associations between periodontitis and rheumatoid arthritis, the use of a mixed approach of

quantitative and qualitative research methods was considered appropriate in order

to develop a better understanding of the specific context of the patient population

that was being investigated.

2 Aims and Objectives

The primary aim of this study was to pilot the feasibility of an interventional trial that aims to evaluate the efficiency of intensive periodontal treatment administered by Dental Hygienists in a secondary care setting to reduce disease activity and improve function for patients with Rheumatoid Arthritis (RA).

To achieve this aim, the following set of objectives was carried out:

- Assess patient recruitment and retention rates

- Refine study protocol and logistics

- Evaluate the efficacy of periodontal treatment using a randomized controlled trial approach in a secondary care setting.

- Evaluate the effects of periodontal treatment on the rheumatoid arthritis disease activity parameters.

    This objective was carried out by monitoring the following clinical outcomes:

    o Disease activity scores (DAS28);

    o Musculoskeletal ultrasound of the joints (Power-Doppler and Gray Scale);

    o Patient reported outcomes: a set of standardized and validated quality of life questionnaires

- Use of qualitative research methods to evaluate the patient's perspectives regarding the relevance and acceptability of the trial

  This objective was carried out by

  - Identifying hindering and encouraging factors for study participation;

  - Tackling the impact of rheumatoid arthritis on the patient's quality of lives the place of oral health on their scale of health priorities.

By using qualitative research methods the project intended to develop a deeper understanding of the values, beliefs and principles of the patients with rheumatoid arthritis. These factors could potentially contribute and shape their decisions regarding their choices to access certain types of health care services.

As for any feasibility study, one of the main endpoints of the OPERA study represented the evaluation of the pre-screening and screening logs together with The CONSORT Diagram (Figure 4 – The CONSORT Flow Diagram) [95, 96]. This was particularly important in order to assess the feasibility of the protocol and together with the qualitative data to tackle the potential problems regarding the implementation of the methodology. Furthermore this could also highlight some important technical and logistic issues and identify possible solutions to overcome these problems. As part of the feasibility findings, it was necessary to get a deeper understanding of the reasons why some of the patients might dropout and to identify the barriers to access and care in order to use this pilot data to develop a larger, statistically powered interventional trial.

3 Rationale for carrying out the study

The Introduction Chapter outlined the current knowledge about the associations between oral health status and systemic conditions as well as the specific associations between periodontitis and rheumatoid arthritis.

The increasing number of publications regarding the associations between oral and systemic conditions reflects the increasing attention of the scientific community towards this topic. However, most of the research performed in this field has used observational designs. The few interventional studies used small sample sizes and were not sufficiently powered to draw any definitive conclusion regarding a causal relationship between exposure and outcome and the effectiveness of periodontal treatment to improve RA outcomes. For all these reasons, it emerged a real necessity to further explore this field by developing a pilot randomized controlled trial (RCT) to assess the feasibility for a larger interventional trial.

The rationale to carry out this study emerged from the need of assessing not only the correlation but also a potentially causal relationship between the two conditions of interest. In order to assess causal relationships between an intervention and outcome, randomized controlled trials are considered the gold standard in clinical research. As it is with any new area of scientific inquiry in clinical research, the theoretical approaches developed by the research community need to reflect the real world setting. The effects of periodontal treatment on patients diagnosed with

rheumatoid arthritis can be assessed from a clinical and biological perspective but some of the specific problems of this patient group cannot be evaluated using purely quantitative methods. The purpose of incorporating qualitative methods was to develop our knowledge and understanding of the specific reasons for patients to participate in the study, to identify potential hindering factors and possible solutions for those and to tackle the acceptability of the intervention for the patients. As part of the feasibility findings, it was necessary to get a deeper understanding of the reasons why some patients might drop-out and to identify the barriers to access and care in order to use this pilot data to develop a larger, statistically powered interventional trial.

Furthermore the outcomes that are relevant for clinicians and researchers might be different for the patients. This could be especially the case for patients that are diagnosed with a chronic condition and might suffer also of a set of specific comorbidities [94, 97, 98]. Understanding the health care priorities of this specific patient population and the importance of oral health on this set of priorities was one of the most important factors in designing the protocol of research project

4 Methodology

4.1 Overview

The OPERA study was a feasibility parallel group randomized controlled clinical trial of the short-term effects of non-surgical periodontal treatment on rheumatoid arthritis disease parameters.

A total of 60 RA patients with chronic periodontitis were randomly allocated to either immediate intervention or control (delayed intervention) group. The intervention consisted of non-surgical periodontal therapy with intensive maintenance therapy delivered by a dental hygienist. Periodontal parameters and RA disease activity parameters were assessed at baseline and at three and six months. At the end of the 6-months study, patients in the control arm were offered the same non-surgical periodontal therapy. Considering that this was a feasibility study, the primary outcome measures were represented by the recruitment and retention rates. The secondary outcome measures provided clinical and non-clinical data about the efficacy of periodontal treatment in patients with rheumatoid arthritis in terms of disease activity and disability, periodontal measures, as well as general and oral-health related quality of life. Moreover, the study included a qualitative assessment, which provided an insight about the acceptability of the intervention and the study procedures from the patients' perspective.

4.2 Study oversight

The Outcomes of Periodontal Therapy in Rheumatoid Arthritis (OPERA) trial took place based on the approval of the National Research Ethics Service (NRES) Committee West Midlands - South Birmingham Research Ethics Committees (REC) Number 11/WM/0235 (Appendix 2), protocol number RG_10-138 (Appendix 1: Study Protocol) and registered via the Integrated Research Application System (IRAS) with project ID 53163.

The recruitment for the trial started in January 2014 and the last patient was randomized in October 2015.

Research and development (R&D) approval was obtained for all the participating sites: Queen Elizabeth Hospital Birmingham (University Hospitals Birmingham NHS Foundation Trust), City Hospital Birmingham (Sandwell and West Birmingham Hospitals NHS Trust), Heartlands Hospital (Heart of England NHS Foundation Trust) and Birmingham Dental Hospital - (Birmingham Community Healthcare NHS Trust.

Heartlands Hospital was the last initiated site. This site had it's own local research team with one rheumatology consultant, one research nurse and one research administrator.

4.3 Study population

The study population was represented by the patients diagnosed with rheumatoid arthritis from The Outpatient Rheumatology Departments from Queen Elizabeth

Hospital Birmingham (University Hospitals Birmingham NHS Foundation Trust), City Hospital Birmingham (Sandwell and West Birmingham Hospitals NHS Trust) and Heartlands Hospital (Heart of England NHS Foundation Trust).

4.4   Recruitment procedures

The rheumatology clinic lists for the follow-up appointments from the participating NHS Trusts were pre-screened by the research team one week in advance. A list of the potentially eligible patients was created by filtering the clinic list, based on the clinical information available in the patient's electronic records. There were minor differences regarding the recruitment procedures in the three different NHS Trusts. While the potentially eligible patients in the Outpatient Rheumatology Department of Queen Elizabeth Hospital Birmingham (University Hospitals Birmingham NHS Foundation Trust), were contacted by post one week before their appointment for follow-up at the rheumatology department, inquiring about their potential willingness to be approached by the research team, the patients from the other 2 NHS Trusts were contacted directly during their follow-up appointments at the rheumatology departments. This decision was taken by the research team at the suggestion of the rheumatology consultants in order to facilitate the recruitment process.

Written information was sent to these patients together with pre-stamped and addressed envelopes, informing them about the research project and the possibility to find out more details, during their visit at the rheumatology clinic. The patients

that returned the letters with a positive answer were approached by the research team and provided with detailed information about the research project.

Patients from City Hospital Birmingham (Sandwell and West Birmingham Hospitals NHS Trust) and Heartlands Hospital (Heart of England NHS Foundation Trust) were approached directly by the research team during their follow-up appointments. The researchers explained the aims of the study, the methodology and the option of free withdrawal at any given time after consenting, without providing any specific reasons. The patients were offered the patients information sheet (see appendixes) and written consent forms.

The recruitment times were Monday mornings for Queen Elizabeth Hospital Birmingham and Tuesday afternoons for City Hospital Birmingham. For the clinics on all the other days of the week, written information was available for the patients at the reception desks and in the consultation rooms together with contact information of the research team).

Those patients that met the inclusion criteria in terms of their rheumatoid arthritis diagnosis, stability of treatment and excluded comorbidities and endentulism and expressed their interest to take part in the study were approached during their follow-up appointments and informed about the possibility of participation in the trial. The patients read the Patient Information Sheet and had the possibility to ask questions and find out detailed information about the trial. Participation in the trial was offered to patients that filled out and signed the Informed Consent Form (see Appendix 6: Informed Consent Form (ICF) Screening. The time and date for the

periodontal screening at Birmingham Dental Hospital, was mutually agreed with the patients for a Wednesday, Thursday or Friday.

The patient's personal details were electronically transferred through the secured NHS email system from the recruitment sites to Birmingham Dental Hospital where new patient notes were created.

4.5 Inclusion criteria

- Ability and willingness to give written informed consent and comply with the requirements of the study protocol.

- Age above 18 years

- Patients with rheumatoid arthritis, diagnosed according to the revised 1987 ACR criteria for the classification of the condition [99]

- DAS28 score ≥3.2 (see paragraph 4.7.3 Disease Activity Score (DAS28)

- DAS28 score >5.1 only if patient on biologics or patient unwilling to take biologics

- Treatment with DMARD for ≥ 3 months and stable dose for ≥ 2 months

- Generalized moderate to severe chronic periodontitis as evidenced by pocketing with clinical attachment loss (CAL>=4 mm on at least 2 non-adjacent teeth AND cumulative probing depth>=40mm) (see paragraph 4.7.4 Periodontal examination) [28, 100]

4.6 Exclusion criteria

- Rheumatic autoimmune disease other than rheumatoid arthritis, or significant systemic involvement secondary to RA (including but not limited to vasculitis, pulmonary fibrosis or Felty's syndrome). Secondary Sjögren's syndrome or secondary limited cutaneous vasculitis with RA was permitted.

- History of, or current, inflammatory joint disease other than RA (including, but not limited to, gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthropathy) or other systemic autoimmune disorder (including, but not limited to, systemic lupus erythematosus, inflammatory bowel disease, scleroderma, inflammatory myopathy, mixed connective tissue disease or any overlap syndrome).

- Diagnosis of juvenile idiopathic arthritis (JIA) or juvenile rheumatoid arthritis (JRA) and/or RA before age 16.

- Any surgical procedure, including bone/joint surgery/synovectomy (including joint fusion or replacement) within 12 weeks prior to baseline or planned during study

- Significant concomitant disease, which would preclude patient participation in the investigators' opinion.

- Intra-articular or parenteral glucocorticoids within 4 weeks prior to baseline

- Any dental condition that would preclude, in the investigator's opinion, participation in the trial (including but not limited to restorations impairing oral hygiene or instrumentation, need for extractions or extensive restorative work)

- Periodontal treatment (surgical or non-surgical, excluding supragingival cleanings) within 12 months prior to baseline

4.7 Clinical assessments

4.7.1 General examination

The general examination consisted on data collection about the patient's height and weight, blood pressure, current medications, medical history and comorbidities, smoking status, alcohol consumption and socio-economic data.

4.7.2 Rheumatologic examination

A trained and calibrated examiner assessed the patient's rheumatoid disease activity using DAS28 (Disease Activity Score).

The training and calibration took part before the start of the recruitment process. The examiner attended several rheumatology consultation clinics at Queen Elizabeth Hospital Birmingham. A specialist in rheumatology assessed the DAS28 score of the patients that accepted to help with the calibration process. The examiner for the research project was instructed about the DAS28 examination process and after several observations, performed blinded examinations on patients. The scores of the examiner were compared with the scores given by the rheumatology specialist. This process was repeated over several weeks, until a good reliability was obtained.

The patients that attended the screening visit at Birmingham Dental Hospital were examined for their DAS28 score. If this score was greater or equal to 3.2 one of the inclusion criteria was fulfilled. In order to qualify for the intervention, the patient needed to be on treatment with disease-modifying anti-rheumatic drugs (DMARD) for at least 3 months and stable dose for at least 2 months before screening.

4.7.3 Disease Activity Score (DAS28)

The 28 joints that were assessed for DAS28 were:

- Shoulder,

- Elbow,

- Wrists,

- 1-5 Metacarpophalangeal (MCP) joints,

- 1-5 Proximal interphalangeal [101] joints,

- Knee

All of which for were assessed for both right and left side of the patient. A calibrated examiner was assessing swelling and tenderness of the examined joints. For each sign of tender joint one point was and for each swollen joint a second point was recorded. Total tenderness and swelling was be calculated and added to the ESR level and the patient's global health self-assessment using a visual analogic scale (VAS) with 0 = best, 100 = worst health status.

DAS28 was calculated using:

$$DAS28 = 0{,}56 * \sqrt{(t28)} + 0{,}28 * \sqrt{(sw28)} + 0.70 * \ln(ESR) + 0.014 * VAS$$

Where:

t28 = number of painful joints from 28 joints

sw28 = number of swollen joints from 28 joints

ESR = erythrocyte sedimentation rate in mm/first hour

VAS = general health or patient's global assessment of disease activity on a 100 mm visual analogic scale [102].

The DAS28 was developed in the early 1980 is The Netherlands and it is widely used ever since as a valid measure of disease activity in both clinical trials and clinical practice in rheumatology [103].

4.7.4 Periodontal examination

A calibrated dentist performed detailed periodontal pocket charting assessing probing pocket depth (PPD) recession level and bleeding on probing. Missing teeth were recorded for each patient and the PPD and recession were recorded on the 4 interproximal sites for each tooth. Periodontal status was assessed using a UNC 15 periodontal probe, after the sampling of gingival crevicular fluid and saliva. In order to be randomized the patients had to present generalized moderate to severe chronic periodontitis as evidenced by pocketing with clinical attachment loss (CAL) greater or equal to 4 mm on at least 2 non-adjacent teeth and cumulative probing depth greater or equal to 40mm. The threshold based on CAL was consistent with the case definition proposed by the CDC/APP working group [104]. Cumulative

pocket depth is the sum of the deepest probing depths of at least 4mm on each tooth [32]. The proposed threshold ensures a minimum number of teeth with deep periodontal pockets, e.g., a patient who had 8 teeth with 5mm pockets met this criterion.

In order to increase the reliability of the findings and considering the large heterogeneity of definitions and thresholds used in studies investigating periodontal disease, additionally percentage of sites with probing pocket depths $\geqslant$ 3mm and probing pocket depths $\geqslant$ 5mm was reported. Furthermore percentage of teeth with probing pocket depths $\geqslant$ 3mm and probing pocket depths $\geqslant$ 5mm were also analyzed as suggested in the most recent literature [30].

The Periodontal Inflamed Surface Area (PISA) is a measure of the disease burden that is aims to quantify the total surface of the inflamed periodontal tissue relative to the number of sites examined and number of teeth that are present [105].

4.8 Patient reported outcomes

In order to evaluate the impact of rheumatoid arthritis and oral health on the different dimensions of the quality of life of the patients, validated questionnaires for the United Kingdom were self-administered by the patients at screening and follow-up visits. The data was collected on scannable, case-report forms developed in Keypoint (2014 Speedwell Software Limited).

The following questionnaires were used:

• Euro-Quol; (Appendix 9)

- Patient Health Questionnaire (PHQ-9); (Appendix 10)

- Oral Health Impact Profile (OHIP) (Appendix 11)

4.8.1 Euro-Quol;

This questionnaire is a widely used, standardized instrument to assess quality of life as a measure of health outcome. It was developed and validated in certain European Union Member States (United Kingdom, The Netherlands and Sweden)[106]

4.8.2 Patient Health Questionnaire (PHQ-9);

PHQ-9 is a reliable and validated questionnaire to assess depression severity. It can be used as an additional measure of psychosocial impact of rheumatoid arthritis over the quality of life of patients living with this condition[107] .

4.8.3 Oral Health Impact Profile (OHIP)

OHIP is a self-administered questionnaire with 14 items, designed to evaluate the impact of oral health over the quality of life of patients. The instrument contains questions, with a high level of reliability and it was used across a large number of studies (Cronbach's α (alpha) = 0.70-0.83) and validity (ANOVA, $p < 0.05$)[108]

4.9 Data management

All the collected data was collected on standardized case report forms (CRF)s as presented in Appendix 9: Case report form. The quality of life questionnaires were

developed using Keypoint (2014 Speedwell Software Limited) and scanned automatically. After scanning the data was manually checked for validity by two independent researchers. The clinical data was collected using CRF's and patient notes. As Birmingham Dental Hospital has moved to a new building during the implementation of this research project, the Governing Body of the Birmingham Community Healthcare NHS Foundation Trust decided that from 01.03.2016 would be no more physical patient notes in the new hospital. All the clinical notes were transferred into the R4 system developed by Carestream Dental. The clinical data collected on the CRF forms was manually imputed in a database developed in Microsoft Access (Microsoft® software) at University of Birmingham, School of Dentistry in 2014. The patient sensitive and confidential data was transferred between the participating NHS Trusts using the secured NHS email system.

4.10 Data monitoring

As this was a feasibility trial with a relatively small sample size, there was no formally constituted Data Monitoring Committee by the Sponsor Organization (University of Birmingham). Data monitoring was done periodically by members of the research team and a midterm audit was performed by an independent clinical researcher.

4.11 Biological samples collection

Biological samples were collected from all screened patients and they were repeated at the 3 months and 6 months follow-up visits for the randomized patients.

4.11.1 Venous blood sampling and processing

From each consented patient were collected 48 ml of blood using red/white (E1480-0304) tubes for serum and green/white (E1480-0302) for plasma. Each tube was labeled with stickers with sample screening number, visit number, time and date. The red/white (E1480-0304) tubes for serum were let to clot for 30 minutes, and then all the tubes were kept on ice for another 30 minutes. Each tube was centrifuged (2680rpm at 4 degrees) for 30mins. The allocated aliquots were 1.5 mls (2 x750ul per tube).

4.11.2 GCF sampling

Gingival crevicular fluid was collected from four sites from the upper right and upper left quadrant (two premolars and two molars) using periopaper strips. (BRAND). Each site was isolated with sulcus cotton rolls and dried with air from triple syringe with 5 blasts buccal and palatal. The direction of the blast was from gingival to occlusal surface. The paper portion of the strip was inserted in the gingival crevice until gentle resistance was felt. The paper strip had to be stable, without falling for 30-seconds and then removed. If the strip has came out during sampling, the site was considered lost. The paper strip was inserted in a pre-

calibrated Periotron 8000 (Oraflow, Plainview, NY) and the readings were recorded

on the CRF form. The 4 paper strips were placed 2 by 2 in cryotubes (Appleton

Woods, Birmingham, U.K.) and dry frozen with liquid nitrogen.

4.11.3 Saliva sampling

The purpose of saliva sampling was to allow the assessment of the presence of

potential biomarkers of periodontal disease and/or systemic diseases. From each

patient 1 ml of saliva was collected using a graded Falcon tube (Corning®, Corning

Incorporated NY) and a sterile marble. Time was recorded, and if the target volume

was not collected during the first 5 minutes, it was allocated another slot of 5 more

minutes. Time was recorded for each 5 minutes necessary to obtain the 1 ml of

saliva. When the target was reached, time and total volume were recorded, and

based on this the flow rate was calculated automatically, when the data was

introduced in the database. The samples were stored on ice, and then centrifuged

at 2500rpm for 10 min to remove debris. The supernatant was transferred into a

cryogenic vial (Greiner Bio-One, UK), without disturbing the pellet. A maximum of

1.8ml was snap frozen in liquid nitrogen and stored in freezer at -80 °C.

4.11.4 Subgingival plaque sampling

The objective was to sample subgingival plaque from up to 6 "representative sites'"

for a patient with periodontitis and 6 sites for a patient with healthy gums or

gingivitis. These sites were as distant as possible from each other, one per sextant,

when possible. The deepest pockets (greater or equal to 4mm) were identified using detailed periodontal charting. For healthy patients or patients with gingivitis with less than 6 eligible pockets, there were selected as many pockets as possible. Once representative teeth have been identified, they were isolated using cotton wools rolls. Supragingival plaque was removed using a cotton wool pledget and air dried.

4.12 Ultrasound

Muskuloscheletal ultrasonography is considered an objective and reliable measurement of RA disease activity [109, 110].

Before the start of recruitment, as part of this study, the researcher was trained and calibrated for the ultrasonic examinations at the Rheumatology Department of the Queen Elizabeth Hospital Birmingham. The researcher observed over several weeks ultrasonic assessments for patients with rheumatoid arthritis performed by a consultant rheumatologist specialised in musculoskeletal ultrasounds. After this, the researcher performed musculoskeletal ultrasonic assessments on healthy volunteers in order to get familiarised with the techniques and recognise the relevant anatomical structures. Following this phase, the researcher performed musculoskeletal ultrasonic assessment of wrists, knuckles and toes of patients diagnosed with rheumatoid arthritis. For each joint, several images longitudinal images were recoreded both in power-doppler and gray-scale format. For each joint a score was given from 0 to 3 whilst 0 representing no active inflammation and

3 representing high level of active inflammation (Table 6 and Table 7). The examination was performed independently both by the researcher and the consultant rheumatologist involved in the training and calibration of the researcher. The scores were compared and the examinations were repeated over several weeks on a large number of patients, until the assessments were presenting a high level of reliability with each other.

The examination technique was developed and validated by the European Society of Musculoskeletal Radiology (ESSR) and used widely in other research projects as well, like APIPPRA (Arthritis Prevention In The Pre-Clinical Phase of RA with Abatacept) [111].

The randomized patients from both groups of this study were assessed at baseline, 3 months and 6 months for grey-scale and power-doppler longitudinal ultrasound of the wrist (Inter-carpal, radio-carpal and ulnar-carpal) and metatarsophalangeal (MCP 1,2,3,4,5) joints. A trained ultrasonographer, blinded for the patients periodontal treatment status, recorded a gray-scale and a power-doppler image on longitudinal view for each joint. Erosions, tenosynovitis and enthesitis was not be recorded in this study.

The power-doppler grading was be based on OMERACT (Outcome Measures in Rheumatology) definitions [112] and the scheme of Szkudlarek [113]

Table 6 -Power-Doppler grading system

Grade	Description
0	Absence of inflammatory signals
1	Isolated signals
2	Confluent signals in less than half of the synovial area
3	Confluent signals in more than half of the synovial area

Table 7 - Gray Scale grading system

Grade	Description
0	Normal view
1	Low grade synovitis. It will be measured the distance from the surface of the bone to the highest vertical point of the synovium)
2	Moderate visible synovitis, not distorting overlying structures
3	marked or very extensive synovitis, or synovitis distorting the overlying extensor tendons and related structures

In the event of isoechoic synovitis (frequently seen in the wrist), the grayscale grade was estimated with the aid of the power-doppler grade if this was available. For example: if the power-doppler was showing active signal of at least grade 1 synovitis, the greyscale image could never be graded as grade 0.

Figure 3 – Gray Scale and Power Doppler images of the wrist

Gray scale	Power Doppler
Right Inter-Carpal longitudinal view	Right Inter-Carpal longitudinal view
Right Ulnar-Carpal longitudinal view	Right Ulnar-Carpal longitudinal view
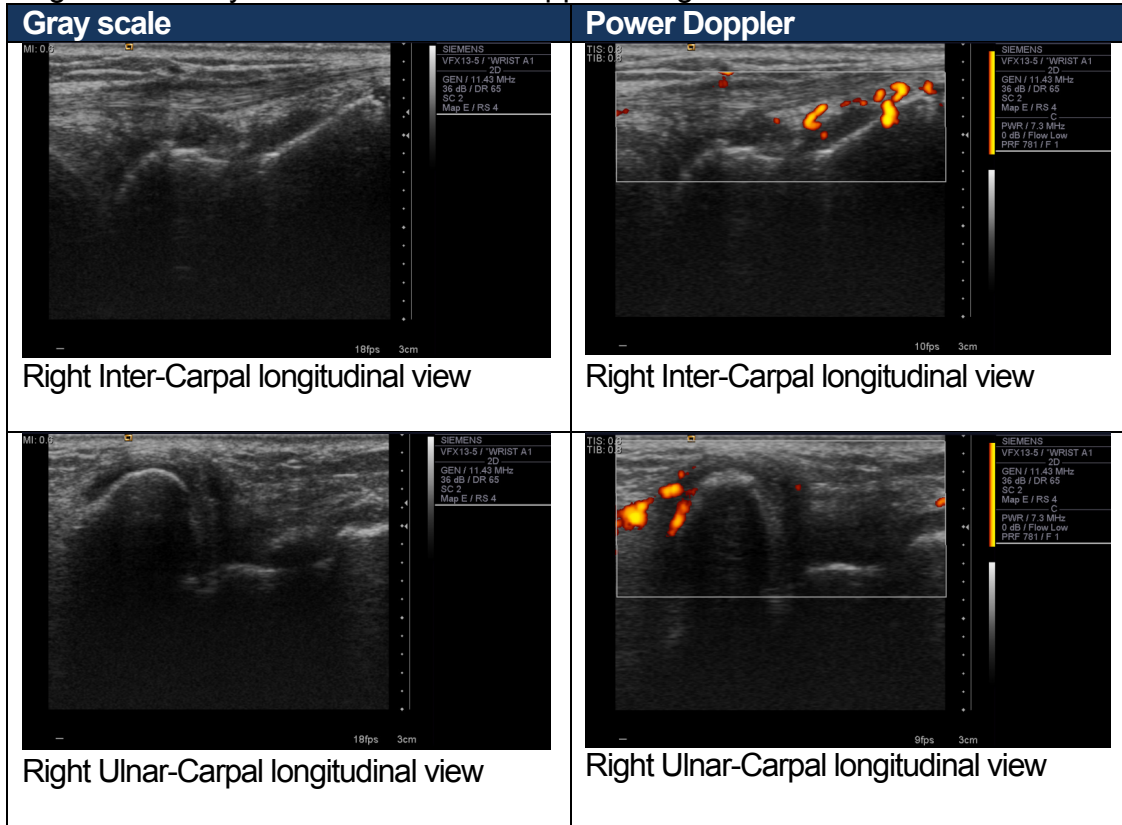
Figure 3 presents an example of Gray Scale and Power Doppler images of the Right Inter Carpal joint and Right Ulnar Carpal joint, both in longitudinal view. The thick, black areas surrounding the epiphysis of the bone in Gray Scale are signs of synovitis as chronic inflammation (not active). The images in Power Doppler are presenting the same bones but with added information regarding the active inflammation (in red).

The grading sheet used for this trial can be found in Appendix 13.

4.13 Randomization

The patients that fulfilled the inclusion criteria and consented for treatment were randomized to one of the intervention arms: immediate treatment or delayed treatment. Birmingham Clinical Trials Unit (BCTU) generated the randomization list. The Treatment allocation was based on stratified randomization by anti-citrulinated protein antibody (ACPA) status (positive or negative).

4.14 Intervention

The patients randomized to the immediate treatment group were invited for treatment appointment with the dental hygienist allocated for this study. When the patients attended this appointment, before seeing the hygienist, a detailed, bilateral musculoskeletal ultrasound was performed as described in section 4.12. The reason for this was to minimize the possibility of influence of treatment at baseline. After the ultrasonic assessment, the patients received their first course of treatment. The treatment consisted of non-surgical periodontal therapy, completed in two or more sessions within three weeks of the baseline. Following oral hygiene instruction, scaling and root surface debridement (RSD) was performed under local anaesthesia using ultrasonic scalers and hand instruments as appropriate. After the follow-up appointments, all sites with greater or equal of 4mm probing depth and bleeding on probing were reinstrumented. The delayed treatment group (control group) received oral hygiene instructions only during the study period. Ultrasonic assessment was performed for this patient group as well, as per the

immediate treatment group. In the event of an increase in probing depth or clinical attachment loss of more than 2 mm (active site) between baseline and follow-up, site-specific rescue treatment was performed. All patients in the control group were offered the same periodontal therapy as the intervention group after study completion (6 months after baseline).

4.15 Follow-up assessments

All patients were followed-up at three months and six months after intervention. At the follow-up visits, the same biological samples, clinical rheumatologic and periodontal examinations and data from the validated questionnaires were collected as at baseline.

4.16 Patients study flow

Table 8 presents the patient study flow. The clinical patient lists for patients who were waiting for their follow-up appointment on the rheumatology clinic from the participating hospitals was pre-screened to identify the potentially eligible patients based on the eligibility criteria presented in paragraph 4.5 Inclusion criteria and paragraph 4.6 Exclusion criteria.

The list of patients created was shared with the nurses and reception personnel that were awaiting the arrival of patients. Occasionally this list was also shared with the rheumatologists in case time allowed it.

The nurses or receptionists asked the patients if they are willing to have a discussion about the research project with a member of the research team while are waiting to be called for consultation. The patients' answers were recorded on the pre-screening sheet. If the patient did not wish to have the discussion but provided reasons for that, those were also recorded on the prescreening sheet.

If the patient agreed to have the discussion, the nurse or receptionist guided the patient to a room where a member of the research team (in most of the cases the author of this thesis) had a discussion with the patient. The patient was presented with the aims and methods of the OPERA study and all the aspects regarding confidentiality were respected. The patient had the possibility to ask questions and which were answered by the researcher. A written informed consent was offered to the patient if he or she decided to participate in the study. The next step was represented by setting up a date and time that was convenient for the patient, to attend the Screening visit at Birmingham Dental Hospital. At this occasion, the patient was asked if any assistance was required for transportation to the Dental Hospital from home or to return. If the patient required assistance, the researcher presented the option of free taxi that was made available through the Trust that operates the Dental Hospital. The researcher checked if the patient had any available ACPA results or ESR. If these were not available, the patient was asked if it would be convenient to have the blood tests done at the rheumatology clinic.

Each patient received a the following documents:

- The Patient Information Sheet for Screening (Appendix 5: Patient Information Sheet (PIS) Scr),

- The written Informed Consent Form (Appendix 6: Informed Consent Form (ICF) Screening)

- Set of quality of life questionnaires (Appendix: 9, 10 and 11)

The patients were asked to complete the questionnaires at home, before the Screening visit and to bring the questionnaires with them to the Dental Hospital at the time of their appointment.

After these steps were completed the patients' details were transmitted through secured NHS email to the Booking Office of Birmingham Dental Hospital. A new patient clinical note was created for each one of the new patients. A reminder letter with the appointment date and time for the Screening visit was sent out by post to each newly booked patient together with the phone number of the researcher in case the patient needed to change the booking on short notice.

One or two days before the appointment, a research nurse called the patients to remind them of their appointment. If they were not available to answer the phone, an answer phone message was left where this was possible.

After the patient arrived to Birmingham Dental Hospital, the patients reported to the reception and were guided to the waiting area for their Screening visit. In case the patients forgot to bring the completed questionnaires with them, they received one to fill out while they were waiting to be seen.

A specially allocated clinic was available for the patients during the time of the OPERA project in the Dental Hospital. The patients were invited for screening and the clinical measurements described in the Methodology chapter were performed.

If the patients fulfilled the eligibility criteria for randomization and treatment, they were explained about the possibility to participate in the interventional phase of the study. The patients were offered written information about the intervention (Appendix 7: Patient Information Sheet (PIS) Treatment and if they agreed to participate, they were offered a written consent form (Appendix 7)

The results of the Screening were completed in the Case report form specially developed for the OPERA project (Appendix 9: Case report form) and in the clinical notes of Birmingham Dental Hospital.

Birmingham Clinical Trials Unit (BCTU) was contacted over telephone and provided a random allocation to one of the treatment arms for the patient, as described in paragraph 4.13 Randomization. If the patient was allocated to the Immediate treatment group, the research nurse from the Periodontology Department booked three appointment with the Hygienist allocated for the project with a maximum three weeks after the Screening visit. If the patient was allocated to the Delayed treatment group, the research nurse booked only one appointment with the Hygienist.

When the patients returned to the Dental Hospital, before meeting the hygienist, the patients from both groups had an approximately half an hour appointment with the author of this thesis for ultrasonic assessment as described in subchapter 4.12 Ultrasound. This was important to avoid the potential contamination of the

ultrasound assessment by the dental hygiene treatment. The author of this study was blind to the treatment allocation status of the patients to assure consistency of the assessment across treatment arms.

After the ultrasonic assessments the patients were accompanied for the first appointment with the Dental Hygienist.

The OPERA study protocol required that the first Follow-up appointment for the Immediate treatment group to be booked at three months after the completion of the non-surgical periodontal treatment. For the Delayed treatment group this was at three months after their one appointment with the Dental Hygienist.

For the first follow-up visit the patients from both groups, completed the same questionnaire and had the same clinical assessments and ultrasound like at the Baseline visit. After the periodontal examination, if the patients from the Immediate treatment group presented the need for more periodontal treatment, a new appointment was booked with the same Dental Hygienist. If the patients from the Delayed treatment group presented a significant increase of their level periodontitis as described in the Protocol, they were offered localized rescue treatment.

The last follow-up appointment was at three months after the second appointment for both groups, or at three months after the completion of periodontal treatment for the cases where this was necessary.

The same quality of life questionnaires and clinical assessments were performed as at the three months appointment. The patients that were part of the Delayed treatment group were offered three appointments with the same Dental Hygienist

for periodontal treatment. All the patients, at the end of the study received £150 to cover the possible costs regarding their time for study participation.

Table 8 - OPERA patient's study flow

Study procedure	Screening		Visit 1 with hygienist	Follow-up 1	Follow-up 2
	Rheumatology Clinic	Dental Hospital			
Informed consent for screening	X	X			
General examination		X		X	X
Inclusion exclusion		X			
Disease Activity Score (DAS28)		X		X	X
Periodontal examination		X		X	X
Quality of life questionnaires		X		X	X
Biological sample collection		X		X	X
Informed consent for treatment		X		X	X
Randomization		X			
Ultrasound			X	X	X
Intervention			X		

4.17 Objectives

4.18 Primary objectives

The primary objective of this pilot study was to assess the feasibility of the intervention, to establish recruitment and retention rates, to gauge the acceptability of the intervention and study procedures to patients. This was achieved through a mixed methods approach of qualitative and quantitative research methods as described in the Methodology section.

4.19 Secondary objectives

The secondary objective was to collect pilot data regarding the efficacy and safety of intensive periodontal therapy and maintenance administered by dental hygienists in a secondary care setting to reduce disease activity and improve function for patients diagnosed with rheumatoid arthritis.

4.20 Statistical analysis

This trial was a pilot study and no formal sample size calculation was required. However, being also a feasibility study, the periodontal treatment that was delivered needed to achieve a minimum level of clinically significant outcome in terms of periodontal healing (pocket probing depths reduction at 3 and 6 months). A reasonable minimum threshold criterion was to expect an effect size of 1 for reduction of mean probing depth. This feasibility study had >90% power to detect such an effect size, even allowing for 20% loss to follow-up. The plan of analysis took into consideration the following endpoints:

- •Periodontal endpoints

- Ultrasound joint scores

- DAS28 scores

- Quality of life questionnaires (OHIP, EQ-5D, PHQ9)

Summary statistics were calculated as appropriate. To test for between group differences at 3 and 6 months, parametric and non-parametric methods were used as appropriate. For continuous variables, differences between groups at 3 and 6 months, adjusted for baseline. For normally distributed endpoints t-test was used and skewed data was analyzed using Mann–Whitney–Wilcoxon test. The categorical variables were analyzed using chi-squared test [114].

All the statistical analysis was performed using StataCorp. 2013. Stata Statistical Software: Release 13. College Station, TX: StataCorp LP.

4.21 Qualitative research methodology

Using qualitative research methods it was possible to get a more detailed insight about the way rheumatoid arthritis affects the life of the patients, as well as their values and perceptions about oral health that could influence their choices to participate in such a study.

4.22 One to one interviews

Semi-structured interviews were designed to include the views of all the patient categories in this study.

These categories were:

a. Patients randomized to the immediate treatment group

b. Patients randomized to the delayed treatment group

c. Patients that were screened but were not eligible for treatment

d. Patients that refused to be screened

Data from the first five patients in these groups was used to design the topic guide for the semi-structured interviews. The initial topic framework that was developed by the research team included: oral health maintenance, treatment preferences (dental and medical), access to dental care, priorities/values placed on oral health, quality of life issues, acceptability of the intervention and, if applicable, reasons for non-participation. The interviews were conducted at Birmingham Dental Hospital, Queen Elizabeth Hospital or over the phone. The interviews were audio recorded

and, subsequently, fully transcribed. Consecutive patients were sampled and the interviews were conducted until saturation was reached. We intended to include subsamples of the patient population as patients who refused to consent for trial participation, patients who were screened but not eligible for randomization, patients who were randomized in the immediate treatment group and patients who were randomized in the control (delayed treatment) group. This ensured a broad range of views and provided a more comprehensive understanding of the subject.

4.23 Qualitative data analysis

A framework approach to data analysis was adopted in the manner suggested by Pope et al. [28] Based on the research questions, was developed a preliminary framework. The transcripts were read and, following familiarization with the data, the initial framework was expanded to reflect themes emerging from the interviews. The data was then indexed according to the framework and further refined. To guard against bias the transcripts were analyzed independently by a second researcher. The findings were presented and consensus was achieved on the emergent themes and issues.

4.24 Qualitative research methodology used in the OPERA study

4.24.1 A brief overview of the methodology

Patients diagnosed with Rheumatoid Arthritis that attended the Outpatient Rheumatology Clinics from Queen Elizabeth Hospital Birmingham, City Hospital Birmingham and Heartlands Hospital Solihull, were approached by members of the research team and offered participation in the OPERA trial. The patients that expressed their interest to find out more about the study were offered written information sheets with detailed description of the study and the members of the research team explained the procedures and the purposes of the research project. The patients had the possibility to ask questions from members of the research team. The patients that agreed to participate were offered written consent form for the screening visit at Birmingham Dental Hospital. A number of patients who did not wish to consent for the screening were offered the possibility to help the project by participating in a qualitative interview, either face to face either over the phone. This was necessary to gather qualitative data about reasons to participate or not in the study and identify potential barriers to access and care that could be addressed by the research team. The patient population that did not wish to participate in the screening for OPERA but agreed to participate in the qualitative interviews was especially important to fulfill the feasibility aim of this study by providing valuable insights in their perceptions about the study, about oral health and about their health care priorities.

All the participants that were interviewed were consented verbally on the recording device. The patients were provided with detailed explanations about confidentiality and their possibility to withdraw anytime from the study. The author conducted semi-structured interviews with the patients, based on the initial topic guide developed by the research team and implemented as pilot with the first three participants.

As new themes emerged from the discussions, the topic guide was constantly adapted and new themes were added until saturation was reached. Saturation was defined as the stage in which no new themes emerged from the interviews and the data started to become mainly repetitive. After saturation, three more interviews were conducted for quality assurance purposes.

The semi-structured interviews were conducted face to face in a room with closed doors to assure privacy. The location was either at the Queen Elizabeth Hospital Birmingham, Rheumatology Outpatients Department, either at Birmingham Dental Hospital. At the first five interviews, a more experienced qualitative researcher that observed the interview process and intervened and provided feedback when necessary accompanied the author of this study. This was important to assure the correct calibration of the interviewer and the accurate implementation of the methodology. For a few patients that preferred the interviews to be conducted over the telephone, the researcher accommodated this request. The reason for this was mainly through time constraints, logistics and convenience on the patient's side.

After the methodology and aims of the qualitative research approach were explained in details to the patients, and the issues related to confidentiality and

freedom for withdrawal from the study was underlined, informed consent was obtained from all the patients.

The semi-structured interviews were recorded on a digital recorder (Olympus VN-713PC Voice Recorder - 4GB Flash Memory, WMA/MP3, Manufacturer Part Number 4545350039745 Black). This was used both for the face to face interviews as well as for the interviews that were conducted over the telephone.

4.25 Topic guide - development and pilot

A multidisciplinary team of experts composed of specialists in rheumatology, qualitative researchers and dentists, developed the initial topic guide before the start of the patient's recruitment in the study. This topic guide was based on the clinical experience of the experts involved in the study and then corroborated with additional topics identified from the literature. This initial topic guide was applied as a pilot with 3 patients that consented to participate. The piloting phase was developed and implemented by the author and an expert in qualitative research to assure the methodological accuracy of the interview process. The results of these 3 interviews were included in the overall findings. Based on the dynamics of the discussions and the flexible structure of the interviews, new themes emerged that were incorporated in the topic guide and added to the interviews with the following participants. Each time a new theme emerged from an interview, this new theme was added to the topic guide and discussed with the next participants.

4.26 Saturation

The semi-structured interview framework allowed the necessary flexibility and freedom for discussion with the participants in order to identify all the possible new themes that could emerge. As new themes emerged, these were added to the topic guide and included in the discussions with new participants. When no more new themes emerged and the discussions started to reach a repetitive status it was considered that saturation was reached. A second researcher, expert in qualitative research methods was involved independently in the data analysis and confirmed the saturation status of the interview process. In order to assure a stronger internal validity, three more interviews were conducted following saturation. No new information emerged from these discussions, as a result saturation was considered to be reached.

4.27 Population sample for the qualitative part of OPERA

For the aims of this study, random purposive sampling was considered the appropriate method of sampling of the participants until saturation was reached. Patients diagnosed with rheumatoid arthritis visiting the Outpatient Rheumatology Clinics from Queen Elizabeth Hospital Birmingham, City Hospital Birmingham and Heartlands Hospital Solihull represented the patient population. The patients were approached by members of the research team and offered detailed information about the research project.

For the qualitative interview process, the patient sample was composed of:

- patients who consented for screening for the clinical research project,

- patients who were found eligible after the screening and were randomized to either the intervention or the control group

- patients who did not consent to be screened for the clinical trial.

4.28 Interviews

The interview process was realized by using a one to one, face to face, semi-structured interview process. The patients were explained initially about the ethical considerations, confidentiality and freedom to withdraw from the study. After the patients consented, the interviews commenced and were recorded on a recording device. The recordings were transcribed without incorporating any personal information from the patients. The transcription was performed by one medical secretary working for Birmingham Dental Hospital. The interviews were conducted in a suitable room, assuring the patients right for privacy and comfort at Queen Elizabeth Hospital and Birmingham Dental Hospital. In a few cases, the patients preferred to have the interview conducted over the phone.

4.29 Analysis

After the interviews were transcribed, data analysis was performed. The transcripts were read carefully and all the new themes that emerged from the discussions were added to the topic guide. The relevant quotes from patients were identified from the transcripts and added to each theme. The data was independently

analyzed by a second researcher, expert in qualitative research methods to assure validity and reliability of the findings.

One of the reasons why this was important was to assure quality and consistency through the data analysis in order to be able to present the findings in a comparable way with the current literature. Another reason was to control for any potential bias in data analysis and interpretation from the author of this thesis thus assuring a higher level of objectivity of the results.

After this topic guide was applied as a pilot for to the first three participants, further topics emerged from the discussions that were included on an on-going basis to the final framework.

The first three topics: Introduction, Rheumatoid arthritis and systemic health and Periodontitis and oral health did not suffer significant changes. The final initial topic guide and the final topic guide can be found in Appendix 16.

5 Results

5.1 Pre-screening

The pre-screening phase of the trial took place in the Rheumatology Outpatient Departments from the Queen Elizabeth Hospital Birmingham (University Hospitals Birmingham NHS Foundation Trust) and City Hospital Birmingham (Sandwell and West Birmingham Hospitals NHS Trust). At a later stage, the Rheumatology Outpatient Department of Heartlands Hospital (Heart of England NHS Foundation Trust) was initiated as well as a recruitment site. The reason for this was to increase the number of patients participating in the study. The first two sites were operated directly by the author of this study, whilst the third site was operated by the members of the research team from the department: one rheumatology consultant, one research nurse and one research administrator.

A pre-screening log was created, as part of the feasibility endpoints to identify the potential number of patients that could be approached for consent and study participation. Information was recorded also regarding the potential causes for refusal of study participation.

Of a total number of 649 patients identified, 296 consented to take part in the screening phase of the trial. The main reason reported by patients for refusing study participation was lack of interest. This was reported by 85 patients.

Other reasons that were reported were edentulism, severe comorbidities that would have impaired study participation, good self-perceived oral health, work and

language barriers. These categories of reasons are presented in Table 9- Pre-screening log. The prescreening log was not available at HEFT

Out of the 296 patients that consented to take part in the screening phase of the trial, 95 did not attend the screening visit as illustrated in Figure 4 – The CONSORT Flow Diagram

Table 9- Pre-screening log

	Total	Total Consent	Total refuse	Refused with reasons					Not eligible (Edent)	Missed
				Comorb	Good OH	Dental phobia	Work	Lang.		
QEHB	290	103	73	52	11	2	6	2	20	80
SWBH	359	182	**45**	33	2	1	3	6	19	109
HEFT*		11								
Total	649	296	**118**	85	13	3	9	8	39	189

QEHB= Queen Elizabeth Hospital Birmingham; SWBH = City Hospital, Birmingham;
HEFT = Solihull Hospital
*Pre-screening log data unavailable at HEFT due to shortage of personnel in the local research team.

5.1.1 Informed refusal

Informed refusal was defined as the patient's choice to refuse consenting for study participation after being informed by one of the members of the research team about the study. Almost half of the patients (85 patients) who refused to participate in the study were part of the informed refusal group. Considering that this is a feasibility study, it was important to tackle the more specific reasons for the phenomena and to get a deeper understanding of the reasons for this choice of the patients. Some of the patients that refused to consent as being part of the informed

refusal group, kindly agreed to be part of the qualitative interview process. The results of those interviews are presented in the Qualitative Results chapter.

5.1.2 Edentulism

The patient's medical history was assessed on the day's clinic list at the Outpatient Rheumatology Departments from the participating NHS Trusts. After identifying the patients who would potentially fulfill the inclusion/exclusion criteria, the patients were approached for informed consent. The medical history of the patients did not contain information regarding the state of their dentition. Edentulism was the second most prevalent cause for not being eligible for consent for study participation. This was reported by 39 patients.

5.1.3 Comorbidities

As described in the Methods Chapter, comorbidities were defined as any condition that would not represent any exclusion criteria but which could potentially preclude study participation from the patient's perspective. These could be severe cardio-vascular conditions, severe respiratory conditions or severe mobility problems. The patients described the fact that because of their comorbidities they already struggle attending several hospital appointments and they do not wish to commit to the research project, which could be a potentially increased burden for them in regards of new hospital appointments at Birmingham Dental Hospital. The comorbidities group was composed of 85 patients.

5.1.4 Good self-reported oral health

A number of patients that were approached for study participation answered that they are happy with their current oral health status and do not wish to participate in the study. Some of these patients described that they do not believe to have periodontal disease or that they believe that in case they would have this condition, their general dental practitioner would have informed them about this and offered them treatment. There were 13 patients in this group.

5.1.5 Work commitments

A small number of patients, in general from a younger age group were unable to consent because of work commitments. These patients reported the fact that their work schedule is not flexible and it would not allow them to attend screening and treatment appointments to Birmingham Dental Hospital.

5.1.6 Language barrier

Language was considered a potential challenge for this study. Some patients that were not fluent in English did consent to participate as they had family members whom were happy to provide translation. As this study had also a component regarding quality of life questionnaires, it was considered unfeasible to offer study participation for patients who did not have any family support that could have offered them help to fill out the questionnaires.

5.1.7 Dental phobia

Three patients reported that they experienced traumatizing events with regards to dental treatment in the past, which lead them to dental phobia. The patients reported that this would make it impossible for them to attend the screening visit at the Dental Hospital.

5.2 OPERA – Patient flow

5.2.1 Recruitment

The first consented patient attended the screening visit on the 01.02.2014. The recruitment stopped with the last patient who was randomized on the 08.10.2015

A number of different recruitment approaches were developed for the OPERA trial, as presented in section 4.4 Recruitment procedures.

5.2.1.1 Letters to request permission for approach

In the beginning of the trial the clinical team from the rheumatology department of Queen Elizabeth Hospital Birmingham, recommended that the patients should be contacted by post, one week prior to their clinical appointment to request their permission to be approached during their clinical appointment regarding study participation. Standard letters were issued together with pre-stamped and pre-addressed response envelopes and these letters were sent to the patient list for the following weeks rheumatology clinics. The standard letters are presented in section 10

Appendix 4: Recruitment letter. The patients had the option of ticking one box if they were happy to be approached by members of the research team or another box if they were not. The letters were sent back to Birmingham Dental Hospital – Oral Surgery Department. The following week, the members of the research team, approached the patients that expressed their permission to be approached in person. A number of issues were identified with this procedure that is presented in section 6.

5.2.1.2 Recruitment posters

As the recruitment days were Mondays and Tuesdays and screening days were Wednesday to Friday, the research team considered developing a poster with basic information about the study and contact details from the investigator. An amendment was submitted for ethical approval (Appendix 2: Ethics Approvals) and after receiving permission recruitment posters were placed in the rheumatology departments of all three participating hospitals (Appendix 13: Recruitment poster)

As the outpatients rheumatology department of Queen Elizabeth Hospital Birmingham is situated in a new building, which is part of a Private Finance Initiative (PFI) with Consort Healthcare Ltd., the recruitment posters for the study were not placed on the corridors and waiting areas because of the technical and financial burden that this would have imposed but they were placed inside the consultation rooms. The poster was designed by the author of this thesis.

In all the other participating NHS Trusts, the recruitment posters were placed in the waiting areas and corridors where patients could easily see them while waiting for their consultations.

In general, the posters were received with interest and enthusiasm from both patients and clinicians. On several occasions, on days when members of the research team were not present in the rheumatology departments, patients contacted a member of the research team via phone to express their interest for study participation. After providing their details, a member of the research team would check their potential eligibility for the study via the clinical portal and contact the patients regarding their potential eligibility for screening.

5.2.1.3 Technical aspects

Birmingham and Black Country Comprehensive Local Research Network (BBC CLRN) requested that all members of the research team that recruited patients across the NHS Trusts should have a research passport set in place. The procedure to obtain took nearly six months however, shortly after this, the BBC CLRN confirmed that this was an administrative failure on their side, as the requirements should have been only for an NHS to NHS letter of access which is a much easier and straight forward procedure. In the beginning of the recruitment phase, the members of the research team were present only in outpatient rheumatology department of Queen Elizabeth Hospital, Birmingham.

In City Hospital and Heartlands Hospital, local research administrators and research nurses did the recruitment initially. As the recruitment was stagnating in these two sites compared to Queen Elizabeth Hospital, after a number of meetings it was decided that members of the recruitment team should also visit City Hospital, Birmingham to assist the local team with the recruitment process. After the author of this thesis was allocated to recruit patients from all sites, the number of patients increased to 10-15 patients for each week from Queen Elizabeth Hospital and City Hospital. This however, only happened after members of the research team personally attended the outpatient rheumatology clinics from the participating NHS Trusts.

Heartlands Hospital (Heart of England NHS Foundation Trust) was the last site that was initiated for recruitment. Here the recruitment was done exclusively by the local research team of the outpatient rheumatology department with aid of the approved recruitment posters.

The patients consented during their routine follow-up visit at the Outpatient Rheumatology Departments of the NHS Trusts that were participating in the study. At this routine visit, the patients were give the written "Patient Information Sheet (PIS) Screening" that provided information regarding the aims and objectives of the study. The PIS described in lay terms the methodology of the study and confirmation of the patients freedom of withdrawal at any point during the study. The patients had the possibility to ask questions about the trial and if they agreed to participate, they were provided with written Informed Consent Forms (ICF). With this occasion they were also offered a time and date that was convenient for them

for the screening visit at Birmingham Dental Hospital (Birmingham Community Healthcare NHS Foundation Trust)

5.2.2 Screening

The screening visit took place at Birmingham Dental Hospital and it was attended by 201 (67.9%) patients of the 296 of the total number of consented patients. A total number of 95 patients failed to attend their screening visit.

5.2.3 Inclusion/Exclusion

From the total number of 201 patients who attended the screening visit 100 (49.7%) did not fulfill the periodontal inclusion criteria. Furthermore, 46 (22.8%) patients did not fulfill the rheumatologic criteria having a rheumatologic disease activity score (DAS28) of less than 3.2.

5.2.4 Randomization

Of the 201 patients that attended the screening visit, 60 were randomized into one of the treatment arms: Immediate or Delayed Treatment. The number of randomized patients was agreed based on the estimates made by the consultant rheumatologists involved in the trial by and consulting the literature as described in the study protocol. The treatment allocation was random and it was operated via a telephone service by Birmingham Clinical Trials Unit (BCTU) - University of

Birmingham. The randomization was stratified based on age, gender, and anti-citrullinated protein antibody (ACPA) values that could be positive or negative.

The first follow-up visit, as described in the methodology chapter, was scheduled at 3 months from baseline for the Delayed Treatment group and 3 months after completion of the periodontal treatment for the Immediate Treatment group.

5.2.5 Loss to follow-up

Visit number two was the first follow-up visit. At this time point 4 patients dropped-out from the Immediate treatment group and 3 patients from the Delayed Treatment group.

The third visit represented the last follow-up visit. This took place at three months from visit number two for the Delayed Treatment group. If patients from the Immediate treatment group required more periodontal treatment as evidenced at the first follow-up visit, the last follow-up visit took place at three months after the completion of this treatment.

The third and last follow-up visit took place at six months from Baseline. One more patient was lost to follow-up in the Delayed Treatment group, which was attended by 26 patients. There were three more patients that were lost to follow-up in the Immediate Treatment group, which in the end had 23 patients (Figure 4 – The CONSORT Flow Diagram)

Figure 4 – The CONSORT Flow Diagram
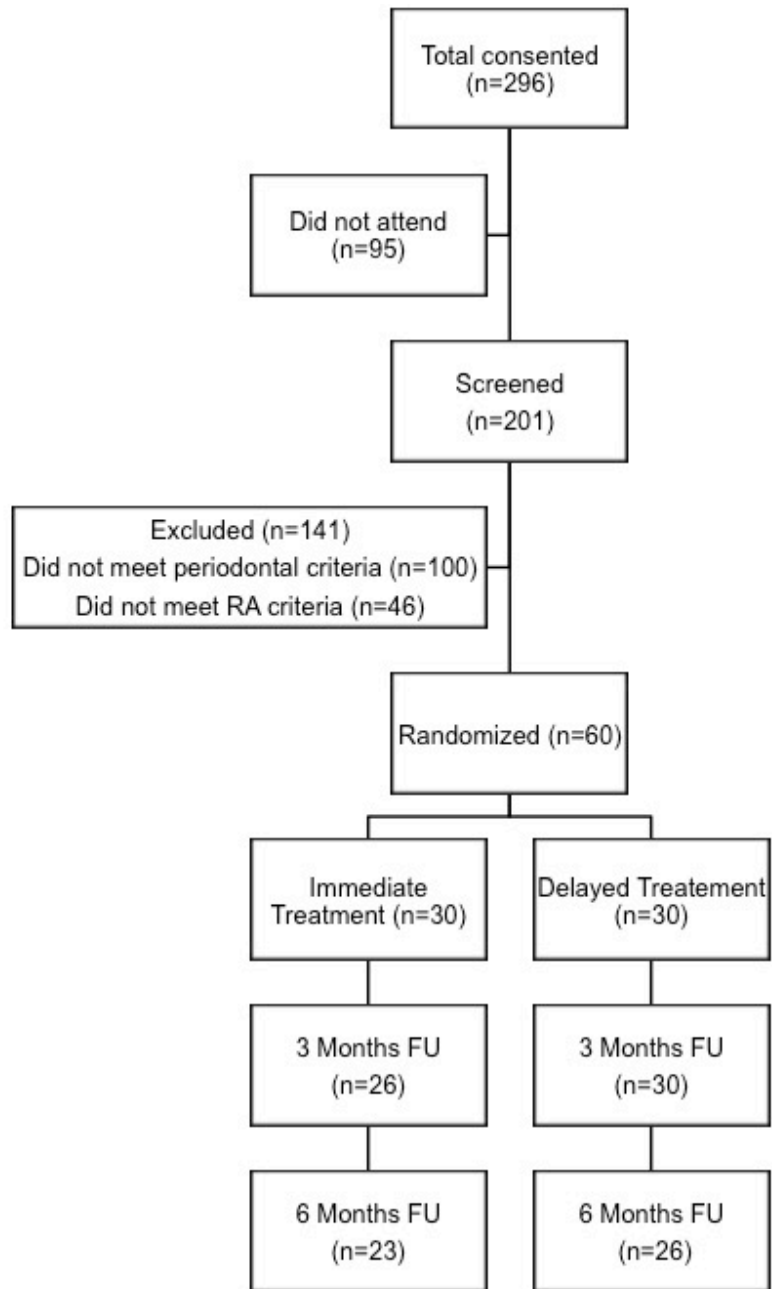
*Some of the Excluded patients did not meet both periodontal and rheumatologic chriteria. The total number of ineligible patients after screening was 141.

5.2.6 Follow-up appointments

Several patients experienced significant delays in their appointments. The study protocol established that after consenting for treatment, the patients were randomized to one of the treatment arms and they received their first appointment with the Dental Hygienist two weeks after the screening visit. In practice this was not always feasible as often patients were not free in the exact given time frame. Furthermore other delays were caused by issues relating to staffing and waiting times at Birmingham Dental Hospital or patients cancelling appointments on short notice without being able to find a new appointment on a close enough time scale. This was especially the case for the first appointment with the Dental Hygienist.

In case a patient failed to attend the appointment with the Dental Hygienist, Birmingham Dental Hospital's policy is to discharge the patient and send a letter to the referring dentist. As the referring dentist for this study was also from the Dental Hospital, if a patient failed to attend the appointment with the Hygienist it often took a long time until the information was forwarded to the members of the research team and they managed to book a new appointment for the patient.

This has led to significant delays for the first appointment with the Hygienist and as a consequence for the first follow-up appointment in the study. As the first follow-up appointment (Visit 2), according to the study protocol should have taken place at three months after the final treatment performed by the Dental Hygienist (for the Immediate Treatment Group) and three months after the one appointment with the Hygienist (for the Delayed Treatment Group) this often took place much later. As illustrated by Table 10 - Time spent between follow-up appointments, it took a

median of 1.5 months for the patients to see the Hygienist for the first time. The protocol required for this period to be no longer than 2 weeks. The treatment for the Immediate treatment group took approximately 2 weeks. These delays lead to an average waiting time of 5 months from Baseline to Visit 2. For the final visit (Visit 3) the delays were less severe with a median of value of 2.9 months for the Immediate treatment group and 3.2 months for the Delayed treatment group. On average a patient spent over eight months as part of the study.

These caused no statistically significant differences between the immediate and delayed group in terms of visit delays.

Table 10 - Time spent between follow-up appointments

Time	Immediate Treatment (n=30)	Delayed Treatment (n=30)	p-value
Baseline- Treatment start, median [IQR] (months)	1.51 [0.93, 2.1]	1.38 [0.98, 2.5]	p=0.794
Treatment duration, median [IQR] (days)	14 [7, 31]	N/A	N/A
Baseline - Visit 2, median [IQR] (months)	5.0 [4.0, 6.6]	4.8 [4.3, 6.8]	p=0.782
Visit 2 - Visit 3, median [IQR] (months)	2.9 [2.7, 3.2]	3.2 [2.5, 3.9]	p=0.286
Overall time in study median [IQR] (months)	8.1 [7.1, 9.4]	8.2 [7.3, 10.5]	p=0.325

Mann-Whitney two-sample test presenting the differences between the two treatment arms in terms of time spent between appointments.
(Median represents the 50% percentile and the interquartile range (IQR) is the 75th percentile minus the 25th percentile.)

5.3   Sample characteristics – Screening

The screening process started on the 01.02.2014 with the first patient screened, and ended with the last patient randomized on the 08.10.2015

Table 11 – Patient characteristics by eligibility

	Eligible (n=60)	Not Eligible (n=141)	p-value
Demographic characteristics			
Age, years	58 [51, 64]	60 [49, 67]	p=0.382
Female, N (%)	45 (75.0)	96 (68.1)	p=0.136
Ethnicity, N (%)			p=0.027
White			
British	30 (50.0)	95 (67.3)	
Irish	1 (1.6)	3 (2.1)	
Any other white	0 (0.0)	1 (0.7)	
White and black Caribbean	1 (1.6)	1 (0.7)	
Any other mixed background	1 (1.6)	0 (0.0)	
Indian	11 (18.3)	5 (3.5)	
Pakistani	6 (10.0)	7 (4.9)	
Bangladeshi	1 (1.6)	0 (0.0)	
Black Caribbean	6 (10.0)	7 (4.9)	
Black African	0 (0.0)	1 (0.7)	
Any other black background	0 (0.0)	1 (0.7)	
Other	1 (1.6)	3 (2.1)	
Missing	2 (3.3)	17 (12.0)	
Smoking status, N (%)			p=0.390
Ex-smoker	18 (30.0)	50 (35.4)	
Never smoked	27 (45.0)	66 (46.8)	
Smoker	15 (25.0)	16 (11.3)	
Missing	0 (0.0)	9 (6.3)	
Smoking amount (cigs/day)	15 (8.7)	14 (9.3)	
Height (m)	1.6 (0.1)	1.7 (0.1)	p=0.026
Weight (kg)	79.9 (20.6)	78.6 (16.8)	p=0.677
BMI	30.0 (7.4)	28.4 (5.9)	p=0.115
SBP (mmHg)	138.6(22.2)	140 (19.6)	p=0.312
DBP (mmHg)	85.8 (13.6)	84.8 (13.6)	p=0.667

Continuous variables are presented as mean (SD) or median [IQR]

Table 12 - Periodontal and rheumatologic outcomes by eligibility

	Eligible (n=60)	Not Eligible (n=141)	p-value
Oral health data			
Median [IQR] number of teeth	23 [19, 26]	24 [20, 27]	p=0.236
Number of sites with periodontal probing depth (PPD) ⩾6mm	6 [1, 8]	1.5 [0, 1]	p<0.001
Proportion of sites/mouth PPD ≥ 3 mm	39 (23)	15 (18)	p<0.001
Proportion of sites/mouth PPD ≥ 5 mm	7 (11)	2 (6)	p<0.001
Proportion of teeth/mouth PPD ≥ 3 mm	68 (23)	32 (26)	p<0.001
Proportion of teeth/mouth PPD ≥ 5 mm	17 (22)	5 (13)	p<0.001
Periodontal Inflamed Surface Area (PISA) mm2	381 [193, 745]	114 [42,333]	p<0.001
Cumulative probing depth	64 [50, 89]	25 [12, 41]	p<0.001
Mean periodontal probing depth (mm)	3.4 (0.7)	2.6 (0.6)	p<0.001
Mean bleeding on probing (% of sites)	30 (22)	17 (18)	p<0.001
Mean clinical attachment loss (mm)	3.8 (1.0)	3 (0.9)	p<0.001
Rheumatologic data			
DAS28	4.9 (1.1)	3.4 (1.4)	p<0.001
ESR	22 (16)	15 (16)	p=0.023
Visual analogue scale (VAS)	60 (21)	41 (27)	p<0.001
Tender joint count	12.1 (8.0)	6.5 (7.3)	p<0.001
Swollen joint count	2.7 (3.2)	1.6 (2.8)	p=0.022
Questionnaire data			
Mean score EuroQuol	12.7 (2.6)	12.0 (2.9)	p=0.140
Mean score Patient Health Questionnaire PHQ-9	11.1 (7.6)	7.7 (7.0)	p=0.007
Mean score Oral Health Impact Profile OHIP-14	14.5 (12.0)	8.8 (10.5)	p=0.002

Variables are presented as mean (SD) or median [IQR]

Table 11 and Table 12 present the demographic characteristics as well as some of the main clinical endpoints for the screened population comparing the characteristics of the randomized patients with the non-randomized ones. The age

of the participants was relatively balanced between eligible and non-eligible patients; the randomized patients group being slightly younger than the not randomized one: the median age for the randomized patients was 58 [51, 64] years whilst for the non-randomized ones was 60 [49, 67] years of age. The median value was the 50% percentile and the interquartile range (IQR) was the 75th percentile minus the 25th percentile.

In terms of gender, women in both groups were representing two thirds of the patients.

In terms of ethnicity, Birmingham area provided a unique opportunity to include patients from several different ethnic backgrounds. Although most of the patients reported to be white British, the group presented a heterogeneous structure encompassing patients from several different ethnic backgrounds. Patients that reported Indian ethnicity, constituted the second most represented patient group in the cohort, followed by Pakistani and Black Caribbean patients.

In terms of blood pressure, both groups presented slightly increased values of blood pressure.

There was no significant difference between the groups regarding smoking habits; both groups consisting of relatively equal percentages of smokers, ex-smokers and patients that reported to be never smokers.

In terms of number of teeth there were no major differences between the randomized vs non-randomized patients.

As expected, based on the inclusion/exclusion criteria of the study, the patients from the randomized group presented significantly higher rheumatologic disease activity and worse periodontal status.

The randomized group presented a slightly higher BMI value compared to the non-randomized one with 30.0 (7.4) versus 28.4 (5.9).

5.4 Sample characteristics for the randomized patients at baseline

Table 13 presents the baseline characteristics for the Immediate treatment and Delayed treatment groups. The treatment group allocation was based on stratified randomization based on gender, age and anti-citrullinated protein antibody (ACPA) status.

Table 13 - Baseline patient characteristics by treatment groups

	Immediate Treatment (n=30)	Delayed Treatment (n=30)
Demographic characteristics		
Age, years	59 [52,65]	57 [50,61]
Female, N (%)	20 (67)	25 (83)
Ethnicity, N (%)		
White		
British	18 (64.3)	12 (40.0)
Irish	0 (0.0)	1 (3.3)
Any other white	0 (0.0)	0 (0.0)
White and black Caribbean	0 (0.0)	1 (3.3)
Any other mixed background	0 (0.0)	1 (3.3)
Indian	4 (14.3)	7 (23.3)
Pakistani	2 (7.1)	4 (13.3)
Bangladeshi	0 (0.0)	1 (3.3)
Black Caribbean	3 (10.7)	3 (10.0)
Black African	0 (0.0)	0 (0.0)
Any other black background	0 (0.0)	0 (0.0)
Other	1 (3.6)	0 (0.0)
Missing	2 (6.7)	0 (0.0)
Smoking status, N (%)		
Ex-smoker	11 (36.7)	7 (23.3)
Never smoked	11 (36.7)	16 (53.3)
Smoker	8 (26.7)	7 (23.3)
Smoking amount	13.1 (7.9)	17.7 (9.4)
Height (m)	1.64 (0.08)	1.62 (0.07)
Weight (kg)	82.8 (22.8)	76.9 (18.1)
BMI	31.0 (7.9)	29.2 (7.0)
SBP (mmHg)	142.6 (21.3)	134.8 (22.8)
DBP (mmHg)	86.8 (14.6)	84.8 (12.8)

Continuous variables are presented as mean (SD) or median [IQR]

Table 14 – Periodontal and rheumatologic outcomes at Baseline by treatment group

	Immediate Treatment (n=30)	Delayed Treatment (n=30)
Oral health data		
Cumulative probing depth	64 [44,80]	64 [56,90]
Mean periodontal probing depth (mm)	3.4 (0.7)	2.6 (0.6)
Mean bleeding on probing (% of sites)	30 (22)	17 (18)
Number of teeth	22 [15, 25]	25 [20, 26]
Number of sites with PPD $\geqslant$ 6mm	5.1 [1, 8]	7 [1, 9]
Proportion of sites/mouth PPD $\geqslant$ 3 mm (%)	40 (22)	38 (24)
Proportion of sites/mouth PPD $\geqslant$ 5 mm (%)	7 (12)	7 (11)
Proportion of teeth/mouth PPD $\geqslant$ 3 mm (%)	71 (20)	66 (21)
Proportion of teeth/mouth PPD $\geqslant$ 5 mm (%)	18 (22)	17 (23)
Periodontal Inflamed Surface Area (PISA) mm^2	374 [180, 745]	390 [203, 720]
Rheumatologic data		
ESR	18 (14)	26 (18)
Visual analogue scale (VAS)	56 (23)	65 (18)
Tender joint count	11.6 (7.9)	12.6 (8.1)
Swollen joint count	2.3 (2.8)	3.1 (3.6)
Mean binarised Power Doppler ultrasound score	3.3 (4.0)	4.7 (4.9)
Mean binarised Gray Scale ultrasound score	5.8 (3.9)	6.6 (4.6)
Mean summary analysis Power Doppler ultrasound score	5.2 (5.6)	7.2 (8.4)
Mean summary analysis Gray Scale ultrasound score	10.0 (6.8)	12.1 (9.7)
Disease-modifying anti-rheumatic drugs (DMARDs), N (%)	11 (36.6)	17 (56.6)
Steroids, N (%)	6 (20)	10 (33.3)
Nonsteroidal anti-inflammatory drugs (NSAIDs), N (%)	3 (10)	6 (20)
Biologics, N (%)	10 (33.3)	10 (33.3)
Mean score EuroQuol	12.5 (2.8)	12.8 (2.5)
Mean score Patient Health Questionnaire PHQ-9	11.4 (7.6)	10.8 (7.7)
Mean score Oral Health Impact Profile OHIP-14	16.2 (13.3)	12.7 (10.6)
ACPA positive N (%)	22 (78.5)	24 (88.8)
ACPA negative N (%)	6 (21.4)	3 (11.1)

Continuous outcomes are presented as mean (SD) or median [IQR]

In terms of age, the two groups were relatively balanced; the patients from the Immediate Treatment group presented a median age of 59 years, whilst the patients from the Delayed Treatment group had a median age of 57 years.

The Delayed Treatment group had slightly more females in terms of percentages (83% vs 67% in the Immediate Treatment group).

In terms of race/ethnicity a similar pattern could be identified as in the comparisons from Table 11. The patients that reported to belong to the White British ethnicity group represented the largest patient population in both arms. They were followed in descending order of number of patients by the patients that reported Indian, Pakistani and Black Caribbean ethnicity,.

As per clinical periodontal characteristics the groups were balanced in terms of cumulative probing depth with a median of 64 mm for each group.

No major differences were observed in terms of BMI, blood pressure or smoking habits.

5.5 Missing data

Table 15 - Missing data by treatment groups

	Immediate Treatment	Delayed Treatment	Total
Periodontal endpoints N (%)			
Baseline	1 (3.33)	0 (0.0)	1 (1.67)
Visit 2	1 (3.85)	0 (0.0)	1 (1.89)
Visit 3	1 (4.35)	0 (0.0)	1 (2.04)
Rheumatologic endpoints N (%) (DAS28)			
Baseline	1 (3.33)	1 (3.33)	2 (3.33)
Visit 2	4 (15.38)	5 (18.52)	9 (16.98)
Visit 3	3 (13.04)	2 (7.69)	5 (10.20)
Rheumatologic endpoints (ultrasonic assessments)			
Baseline	2 (6.67)	3 (10.00)	5 (8.33)
Visit 2	2 (7.69)	0 (0.0)	2 (3.77)
Visit 3	0 (0.0)	2 (7.69)	2 (4.08)
EuroQuol N (%)			
Baseline	5 (16.67)	2 (6.67)	7 (11.67)
Visit 2	7 (26.92)	5 (18.52)	12 (22.64)
Visit 3	8 (34.78)	6 (23.08)	14 (28.57)
Patient Health Questionnaire N (%)			
Baseline	6 (20.00)	5 (16.67)	11 (18.33)
Visit 2	9 (34.62)	12 (44.44)	21 (39.62)
Visit 3	11 (47.83)	10 (38.46)	21 (42.86)
Oral Health Impact Profile N (%)			
Baseline	4 (13.33)	5 (16.67)	9 (15.00)
Visit 2	7 (26.92)	7 (26.93)	14 (26.42)
Visit 3	8 (34.78)	9 (34.62)	17 (34.69)
Medication changes Baseline-Visit 2 N (%)	13 (48.15)	12 (44.44)	25 (46.30)
Medication changes Baseline-Visit 3 N (%)	15 (59.26)	12 (44.44)	28 (51.85)

The missing data is presented only for the randomized patients in Table 15. One randomized patient had missing periodontal measurements at Baseline and Follow-up visits.

In terms of rheumatologic endpoints, 2 (1.89%) patients had missing data at Baseline, one in each group. Furthermore for Visit 2, there were 4 (15.38%) patients for the Immediate Treatment group and 5 (18.52%) for the Delayed Treatment group. For Visit 3, there were 3 (13.04%) patients for the Immediate Treatment group and 2 (7.69%) patients for the Delayed Treatment group with missing data.

In terms of ultrasonic assessments at Baseline, 2 (6.67%) patients from the Immediate Treatment group and 3 (10.00%) from the Delayed Treatment group had missing data. Only 2 (7.69%) patients from the Immediate Treatment group had missing data for Visit 2 and 2 (7.69%) patients had for Visit 3.

The EuroQuol questionnaire at Baseline was not completed by 5 (16.67%) patients from the Immediate Treatment group and 2 (6.67%) of the patients from the Delayed Treatment group.

For Visit 2 there were 7 (26.92%) patients in the Immediate Treatment group and 5 (18.52%) in the Delayed Treatment group who failed to complete the questionnaire. For the last Follow-up Visit there were 8 (34.78%) patients in the Immediate Treatment group and 6 (23.08%) in the Delayed Treatment group with missing data from the EuroQuol questionnaires.

A similar tendency was present with the Patient Health Questionnaire and the Oral Health Impact Profile.

There is no information regarding medication changes for 25 patients (46.30%) from Baseline to Visit 2 and for 28 patients (51.85%) from Visit 2 to Visit 3.

This is because the information regarding the changes in medications was obtained by screening the clinical letters from the rheumatology clinics from all the randomized patients from the moment they consented to take part in the trial, until the moment they finished the trial. This information was sometimes difficult to obtain as some of the patients did not have a large number of clinical appointments at the rheumatology clinics and some of the patients were seen by their general practitioners. The information that was available was presented in the section – Medication changes.

5.6 Clinical outcomes

5.6.1 Periodontal parameters at baseline

The periodontal endpoints measured at baseline were represented by cumulative probing depth (mm), mean periodontal probing depth, (mm) mean bleeding on probing (% of sites) and mean clinical attachment loss (mm). Additionally number of teeth, proportion of sites per mouth with periodontal probing depth greater or equal with 3 mm and proportion of sites per mouth with periodontal probing depth greater or equal with 5 mm were also calculated to provide a more precise overview about the clinical data. For a more generalized overview, proportion of teeth per mouth with periodontal probing depth greater or equal with 3 mm and respectively 5 mm were also calculated. The Periodontal Inflamed Surface Area (PISA) calculated in mm^2 was also considered as a clinically relevant outcome. These findings are presented in Table 16 - Periodontal parameters at baseline between treatment arms.

The two groups were relatively balanced at baseline in terms of cumulative and mean probing depth. The Immediate treatment group had a larger proportion of active bleeding sites compared to the Delayed treatment group (34% vs. 26%).

In terms of median number of teeth between treatment groups, patients from the Delayed Treatment group had a larger number of teeth compared to the Immediate Treatment group. Most of the periodontal values measured at baseline were relatively balanced between the two treatment arms.

Table 16 - Periodontal parameters at baseline between treatment arms

	Immediate Treatment (n=30)	Delayed Treatment (n=30)
Cumulative probing depth	64 [44,80]	64 [56,90]
Mean periodontal probing depth (mm)	3.4 (0.7)	3.3 (0.7)
Mean bleeding on probing (% of sites)	34 (26)	26 (16)
Mean clinical attachment loss (mm)	4.0 (1.0)	3.6 (0.9)
Number of sites with PPD ⩾6mm	5.1 [1, 8]	7 [1, 9]
Number of teeth	22 [15, 25]	25 [20, 26]
Proportion of sites/mouth PPD ⩾ 3 mm (%)	40 (22)	38 (24)
Proportion of sites/mouth PPD ⩾ 5 mm (%)	7 (12)	7 (11)
Proportion of teeth/mouth PPD ⩾ 3 mm (%)	71 (20)	66 (21)
Proportion of teeth/mouth PPD ⩾ 5 mm (%)	18 (22)	17 (23)
Periodontal Inflamed Surface Area (PISA) mm^2	374 [180, 745]	390 [203, 720]

Continuous outcomes are presented as mean (SD) or median [IQR]

5.6.2 Periodontal parameters at follow-up

Table 17 - Periodontal parameters between treatment arms at follow-up, illustrates all the clinical periodontal endpoints between the two treatment arms between the baseline and the follow-up visits. The statistical significance of these mean differences was calculated using two-sample t test for continuous variables, which were normally distributed, and two sample Wilcoxon (Mann-Whitney) test for. Skewed distributions. A summarized overview of the periodontal endpoints from Baseline to Visit 3 are presented in Table 17 and Table 18.

Table 17 - Periodontal parameters between treatment arms at follow-up (1)

	Immediate Treatment	Delayed Treatment	p-value
Cumulative probing depth (mm)			
Baseline	64 [44,80]	64 [56,90]	N/A
Visit 2	42 [22,68]	87 [68,106]	**0.002**
Visit 3	33 [21,73]	81 [54,94]	**0.002**
Mean probing depth (mm)			
Baseline	3.4 (0.7)	3.3 (0.7)	N/A
Visit 2	3.1 (0.9)	3.5 (0.7)	0.085
Visit 3	3.1 (0.8)	3.3 (0.6)	0.185
Mean BOP (% of sites)			
Baseline	34 (26)	26 (16)	N/A
Visit 2	19 (14)	27 (21	0.108
Visit 3	16 (17	23 (19)	0.189
Mean CAL (mm)			
Baseline	4.0 (1.0)	3.6 (0.9)	N/A
Visit 2	4.0 (1.4)	3.9 (0.9)	0.646
Visit 3	4.0 (1.3)	3.7 (0.7)	0.425
Number of teeth			
Baseline	22 [15, 25]	25 [20, 26]	N/A
Visit 2	23 [15, 26]	25 [19, 27]	p=0.059
Visit 3	21[14, 24]	24 [19, 27]	**p=0.035**
Number of sites ≥ 6mm			
Baseline	5.1 [1, 8]	7 [1, 9]	N/A
Visit 2	4.5 [0, 1]]	7.9 [2, 9]	**0.003**
Visit 3	3.5 [0, 1]	5.8 [0, 3]	0.095

Continuous outcomes are presented as mean (SD) or median [IQR]

For non-normally distributed outcomes, Mann-Whitney two-sample test tests the difference between the two treatment arms in terms of periodontal characteristics from Baseline to Visit 3. For normally distributed outcomes, t-test tests the same comparison.

Table 18 - Periodontal parameters between treatment arms at follow-up (2)

	Immediate Treatment	Delayed Treatment	p-value
Proportion of sites/mouth PPD ≥ 3 mm (%)			
Baseline	40 (22)	38 (24)	N/A
Visit 2	29 (27)	43 (21)	**p=0.006**
Visit 3	27 (23)	39 (21)	**p=0.028**
Proportion of sites/mouth PPD ≥ 5 mm (%)			
Baseline	7 (12)	7 (11)	N/A
Visit 2	5 (12)	8 (10)	**p=0.007**
Visit 3	5 (14)	5 (7)	p=0.213
Proportion of teeth/mouth PPD ≥ 3 mm (%)			
Baseline	71 (20)	66 (21)	N/A
Visit 2	48 (28	74 (20	**p=0.001**
Visit 3	53 (29	66 (22)	p=0.107
Proportion of teeth/mouth PPD ≥ 5 mm (%)			
Baseline	18 (22)	17 (23)	
Visit 2	13 (25)	20 (19)	**p=0.008**
Visit 3	13 (21)	15 (17)	p=0.170
Periodontal Inflamed Surface Area (PISA) mm2			
Baseline	374 [180, 745]	390 [203, 720]	
Visit 2	195 [96, 350]	376 [192, 907]	**p=0.030**
Visit 3	110 [35, 328]	308 [102, 871]	p=0.060

Continuous outcomes are presented as mean (SD) or median [IQR]

For non-normally distributed outcomes, Mann-Whitney two-sample test tests the difference between the two treatment arms in terms of periodontal characteristics from Baseline to Visit 3. For normally distributed outcomes, t-test tests the same comparison.

5.6.2.1 Cumulative probing depth

The groups were balanced at baseline with 64 [44,80] mm for the Immediate treatment group and 64 [56, 90] mm for the Delayed treatment group (Table 17).

At Visit 2 this value decreased for the Immediate treatment group to 42 [22, 68] mm and increased to 87 [68, 106] for the Delayed treatment group. This was statistically a significant difference between the groups (p = 0.002). The same trend was observed for Visit 3 where the Immediate treatment group presented a median value of 33 [21,73] mm and the Delayed treatment group presented 81 [54,94] mm. In this case as well, the results were statistically significant (p = 0.002) and the null hypothesis was rejected.

Figure 5 presents the median values for cumulative probing depth (mm) between treatment groups from Baseline to the Follow-up visits

Figure 5 - Median cumulative probing depth (mm)
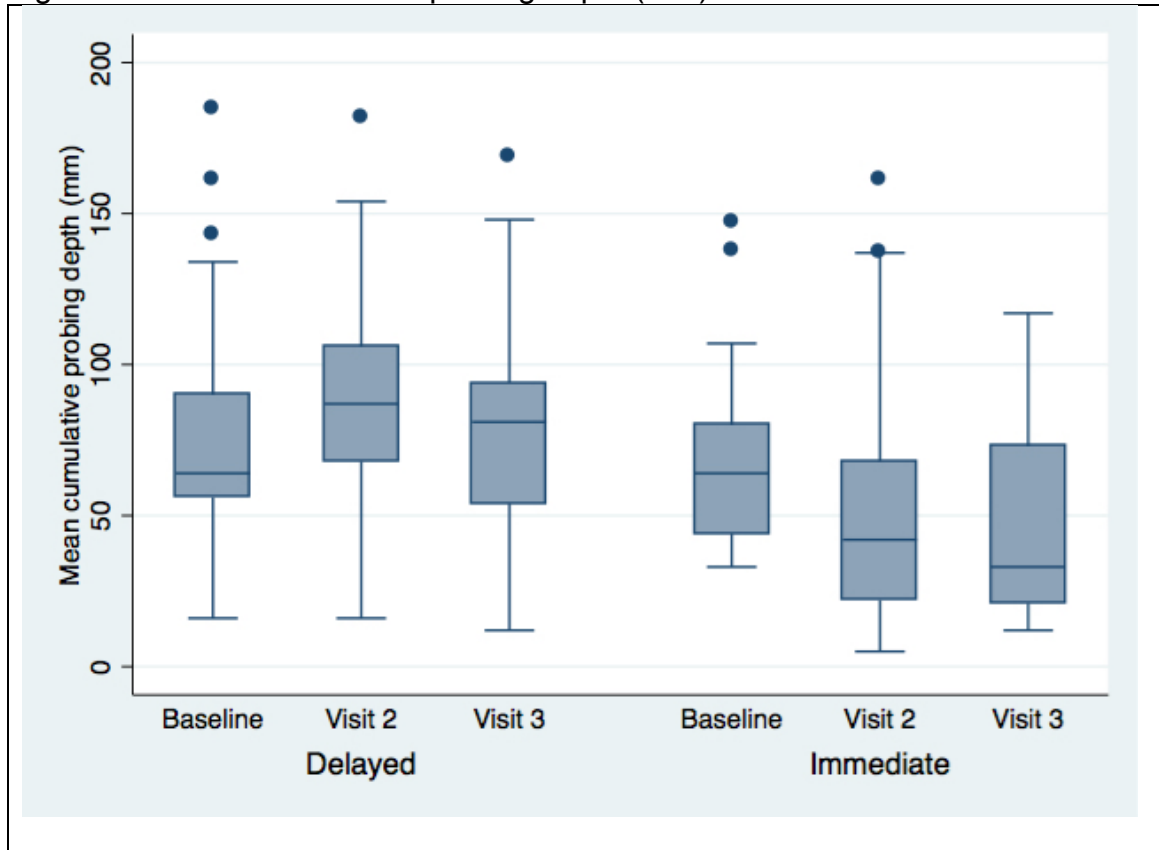
Box and whisker plot of the cumulative probing depths between the treatment arms and visits
The median value represents the 50% percentile and the interquartile range (IQR) is the 75th percentile minus the 25th percentile. The dots are representing the outliers.

5.6.2.2 Mean periodontal probing depth

Figure 6- Median periodontal probing depth (mm) illustrates the effect of periodontal treatment in terms of mean periodontal probing depth, between baseline and the two follow-up visits, comparing the mean values between the Immediate treatment group and the Delayed treatment group. At visit number one (baseline) the two groups presented a mean value for periodontal probing depth of

3.4 mm for the immediate treatment group and 3.3 mm for the delayed treatment group.

This value decreased at the follow-up visit for the Immediate treatment group to 3.1 mm at visit 2 and remained constant for visit 3. In the case of the Delayed treatment group, the mean periodontal probing depth presented a slight increase, from 3.3 mm at baseline to 3.5 mm for visit 2 and 3.3 mm at visit 3. These values were not statistically significant (p = 0.085 for Visit 2 and p=0.185 for visit 3).

Figure 6- Median periodontal probing depth (mm)
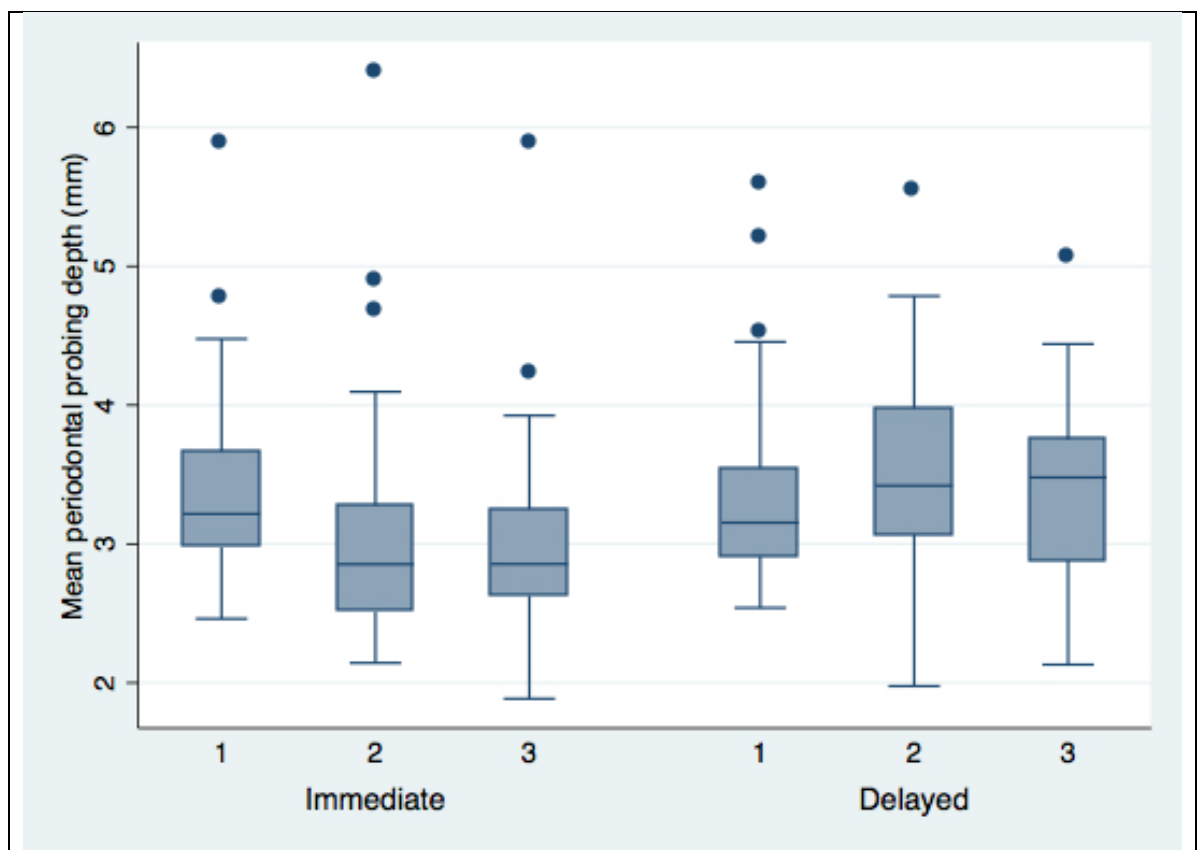
Box and whisker plot of the periodontal probing depths between the treatment arms and visits

5.6.2.3 Mean clinical attachment loss (CAL)

Clinical attachment loss was calculated as the difference between periodontal probing depth and recession expressed in millimeters. The mean values at Baseline were 4.0 (1.0) mm for the Immediate treatment group and 3.6 (0.9) mm for the delayed treatment group. This value remained constant for the Immediate treatment group 4.0 (1.4) mm at Visit 2 and 4.0 (1.3) mm and Visit 3. For the Delayed treatment group the mean CAL presented a slight increase to 3.9 (0.9) mm at Visit 2 and 3.7 (0.7) mm at Visit 3. These differences were not statistically significant (p = 0.646 for Visit 2 and p = 0.425 for Visit 3). Figure 7 presents a box and whisker plot regarding the changes in mean clinical attachment loss from baseline to follow-up visits between treatment groups.

Figure 7 - Median Clinical attachment loss (mm)
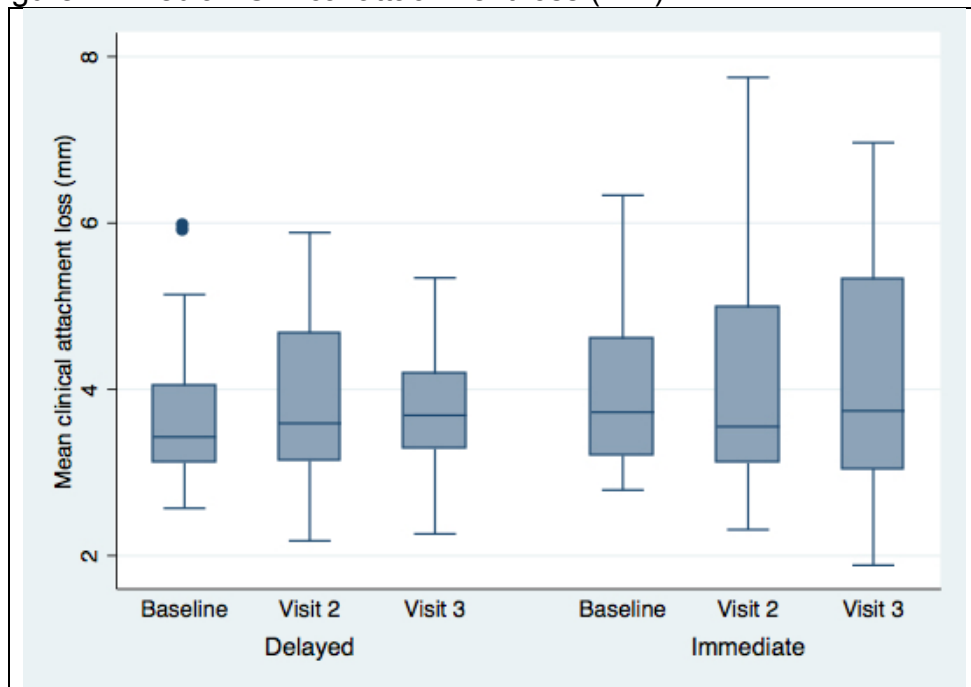
Box and whisker plot of the clinical attachment loss between the treatment arms and visits

5.6.2.4 Bleeding on probing (BoP)

Mean bleeding on probing was expressed as a percentage of active bleeding sites. As presented in Figure 8 and Table 17 this was slightly higher at Baseline in the Immediate treatment group (34% of sites bleeding) compared to the Delayed treatment group (26% of sites bleeding). The mean values presented a decreasing tendency in both groups. The Immediate treatment group mean bleeding on probing values decreased to only 19% of sites for Visit 2 and 15% for Visit 3 whilst the Delayed treatment group presented a decrease of the mean values to 27% for Visit 2 and 23% for Visit 3. None of these, however, was statistically significant ($p = 0.108$ for Visit 2 and $p = 0.189$ for Visit 3).

Figure 8 -Median bleeding on probing (percentage of sites)
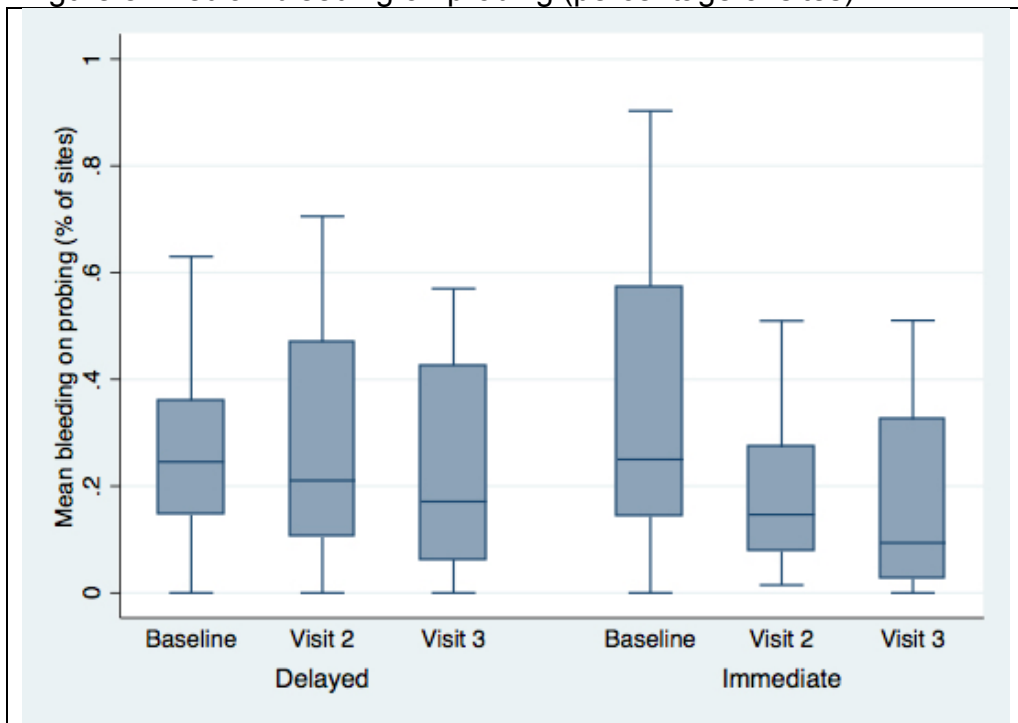
Box and whisker plot of the bleeding on probing between the treatment arms and visits

5.6.2.5 Number of teeth

Patients from the Immediate Treatment group had slightly less teeth present than those from the Delayed Treatment group. The differences, where not statistically significant at Baseline nor at Visit 2. The data presented statistically significant difference for Visit 3 (Table 19).

Table 19 - Number of teeth by treatment group at each visit

	Number of teeth, median [IQR]		
	Baseline	Visit 2	Visit 3
Immediate Treatment	22 [15, 25]	23 [15, 26]	21 [14, 24]
Delayed Treatment	25 [20, 26]	25 [19, 27]	24 [19, 27]
p-value	p=0.059	p=0.064	p=0.035

Mann-Whitney two-sample test for the difference in the number of teeth at each visit between the two treatment arms

5.6.2.6 Number of deep periodontal pockets

The number of deep periodontal pockets, or deep sites with periodontal probing depth (PPD) ≥ 6 mm decreased after Visit 2 in the Immediate Treatment group. This was statistically significant. For Visit 3, difference however the difference lost it's statistical significance (Table 20)

Table 20 - Number of deep periodontal pockets

	Number of deep periodontal pockets		
	Baseline	Visit 2	Visit 3
Immediate Treatment	5.1 [1, 8]	4.5 [0, 1]	3.5 [0, 1
Delayed Treatment	7 [1, 9]	7.9 [2, 9]	5.8 [0, 3]
p-value	p=0.815	**p=0.003**	p=0.095

Mann-Whitney two-sample test for the difference in the number of deep periodontal pockets at each visit between the two treatment arms

5.6.2.7 Proportion of sites/mouth with PPD ≥ 3mm

Table 21 presents the mean proportion of sites per mouth with periodontal probing depth of 3 mm or more (shallow pockets). The proportion of these sites decreased at Visit 2 and Visit 3, compared to Baseline in the Immediate Treatment group. This change was statistically significant.

Table 21 -Proportion of sites/mouth PPD ⩾ 3 mm by treatment group at each visit

	Proportion of sites/mouth PPD ≥ 3 mm (%), mean (SD)		
	Baseline	Visit 2	Visit 3
Immediate Treatment	40 (22)	29 (27)	27 (23)
Delayed Treatment	38 (24)	43 (21)	39 (21)
p-value	p=0.485	**p=0.006**	**p=0.028**

Two-sample t-test for the difference in the proportion of sites ⩾ 3 mm at each visit between the two treatment arms

5.6.2.8 Proportion of sites/mouth with PPD ≥ 5 mm

Table 22 presents the mean proportion of sites per mouth with periodontal probing depths of 5 mm or more. The patients from both groups had a small proportion of pockets that were greater or equal to 5 mm. It can be observed that there is a statistically significant decrease of the mean proportion of deep pockets in the Immediate treatment group, after Baseline treatment at Visit 2. There was no statistically significant change in terms of the mean proportion of deep pockets for Visit 3. The Delayed treatment group presented an increase of the mean proportion of deep pockets from Baseline 7 (11) % to Visit 2 - 8 (10) %. This was followed by a decrease to 6 (7) % at Visit 3 which was not statistically significant.

Table 22 -Proportion of sites/mouth PPD ⩾ 5 mm by treatment group at each visit

	Proportion of sites/mouth PPD ≥ 5 mm (%), mean (SD)		
	Baseline	Visit 2	Visit 3
Immediate Treatment	7 (12)	6 (14)	5 (12)
Delayed Treatment	7 (11)	8 (10)	6 (7)
p-value	p=0.720	**p=0.006**	p=0.189

Two-sample t-test for the difference in the proportion of sites ⩾ 5 mm at each visit between the two treatment arms

5.6.2.9 Proportion of teeth/mouth PPD ≥ 3mm

The proportion of teeth per mouth with pockets greater than the established threshold (shallow pockets) is a less precise measure than the proportion of sites per mouth. This, however, contributes to the general description of the clinically relevant endpoints.

Table 23 presents the mean proportion of teeth per mouth with periodontal probing depth of 3 mm or more. It can be noticed a consistent reduction of this endpoint in the Immediate Treatment group. The statistical significance could be proved only for Visit 2.

Table 23 - Proportion of teeth/mouth PPD ⩾ 3 mm by treatment group at each visit

	Proportion of teeth/mouth PPD ≥ 3 mm (%) mean (SD)		
	Baseline	Visit 2	Visit 3
Immediate Treatment	71 (20)	48 (28)	53 (29
Delayed Treatment	66 (21)	74 (20)	66 (22)
p-value	p=0.342	**p=0.001**	p=0.107

Two-sample t-test for the difference in the proportion of teeth with sites ⩾ 3 mm at each visit between the two treatment arms

5.6.2.10   Proportion of teeth/mouth PPD ≥ 5mm

Table 24 presents the proportion of teeth per mouth with periodontal probing depth of 5 mm or more. As in the previous table, here as well it can be observed a statistically significant difference between Immediate Treatment and Delayed Treatment at Visit 2.

Table 24 -Proportion of teeth/mouth PPD ⩾ 5mm by treatment group at each visit

	Proportion of teeth/mouth PPD ≥ 5 mm (%) mean (SD)		
	Baseline	Visit 2	Visit 3
Immediate Treatment	18 (22)	13 (25)	13 (21)
Delayed Treatment	17 (23)	20 (19)	15 (17)
p-value	p=0.680	**p=0.008**	p=0.170

Two-sample t-test for the difference in the proportion of teeth with sites ⩾ 5 mm at each visit between the two treatment arms

5.6.2.11   PISA (Periodontal Inflamed Surface Area)

Table 25 presents the Periodontal Inflamed Surface Area (PISA) as median values in mm^2 with interquartile range [IQR]. This measure shows the two treatment arms being relatively balanced at Baseline with a consistent and statistically significant reduction at Visit 2 and Visit 3 for the Immediate Treatment group.

Table 25 -PISA (Periodontal Inflamed Surface Area) by treatment group at each visit

	PISA (Periodontal Inflamed Surface Area (mm^2), median [IQR]		
	Baseline	Visit 2	Visit 3
Immediate Treatment	374 [180, 745]	195 [96, 350]	110 [35, 328]
Delayed Treatment	390 [203, 720]	376 [192, 907]	308 [102, 871]
p-value	p=0.933	p=0.030	p=0.06

Mann-Whitney two-sample test for the difference in PISA at each visit between the two treatment arms

5.6.3 Rheumatologic outcomes – DAS28

The clinical outcomes that were monitored from a rheumatologic perspective consisted of the rheumatoid arthritis disease activity score (DAS28) and musculoskeletal ultrasound. The Methods Chapter described in detail the data collection process for these clinical endpoints. The mean value of DAS28 was higher in the Delayed treatment group. The calculation methods for DAS28 were described in more detail in the Methods Chapter. The components of the DAS28 score are the total number of swollen and tender joints, erythrocyte sedimentation rate (ESR) and the 'Patient Global' Visual Analogue Scale (VAS). Each of these components are presented below.

The mean values of DAS28 decreased in both groups between baseline and follow-up visits as presented in Table 26 - Mean DAS28 . This, however, was not statistically significant.

Table 26 - Mean DAS28 scores by treatment group at each visit

DAS28	Immediate Treatment , mean (SD)	Delayed Treatment, mean (SD)	p-value
Baseline	4.6 (1.0)	5.1 (1.1)	N/A
Visit 2	4.2 (1.2)	4.8 (1.5)	0.145
Visit 3	4.2 (1.6)	4.9 (1.3)	0.112

Two-sample t-test for the difference in the mean DAS28 at each visit between the two treatment arms

5.6.3.1 Erythrocyte sedimentation rate (ESR)

Table 27 - presents the mean values for the erythrocyte sedimentation rate (ESR) as a component of the rheumatoid arthritis disease activity score (DAS28). The Delayed treatment group presented a higher value at Baseline compared to the Immediate treatment group. Any difference between the two groups at baseline was considered as random; therefore no statistical test was performed.

Table 27 - Mean ESR by treatment group at each visit

ESR	Immediate Treatment, mean (SD)	Delayed Treatment, mean (SD)	p-value
Baseline	18 (14)	26 (18)	N/A
Visit 2	16 (12)	19 (15)	0.364
Visit 3	16 (12)	22 (13)	0.179

Two-sample t-test for the difference in the mean ESR at each visit between the two treatment arms

5.6.3.2 Patients Global Visual Analogue Scale (VAS)

Table 28 - presents the mean values for the 'Patient Global' Visual Analogue Scale (VAS) as a component of the rheumatoid arthritis disease activity score (DAS28). Also in this case, the Delayed treatment group presented a higher value at Baseline compared to the Immediate treatment group. The differences between the treatment groups at follow-up were only significant for visit 3. The interpretation of the results was elaborated in the Discussions Chapter.

Table 28-Mean VAS by treatment group at each visit

VAS	Immediate Treatment, mean (SD)	Delayed Treatment, mean (SD)	p-value
Baseline	56 (23)	65 (18)	N/A
Visit 2	56 (20)	66 (18)	0.068
Visit 3	50 (26)	67 (20)	**0.022**

Two-sample t-test for the difference in the mean VAS at each visit between the two treatment arms

5.6.3.3 Tender joints count

The mean value of the tender joint count was calculated for each group of patients.

Table 29 presents their mean values and their statistical significance.

Table 29 - Mean tender joint count by treatment group at each visit

Tender joints count	Immediate Treatment, mean (SD)	Delayed Treatment, mean (SD)	p-value
Baseline	11.6 (7.9)	12.6 (8.1)	N/A
Visit 2	8.8 (6.4)	12.5 (8.9)	0.089
Visit 3	9.2 (7.0)	11.8 (7.9)	0.231

Two-sample t-test for the difference in the mean tender joint count at each visit between the two treatment arms

5.6.3.4 Swollen joints count

Table 30 presents the mean values for swollen joints count as a component of the rheumatoid arthritis disease activity score (DAS28). Also in this case, the Delayed treatment group presented a higher value at Baseline compared to the Immediate treatment group. The differences between the treatment groups at follow-up were not statistically significant.

Table 30 -Mean swollen joint count from baseline to follow-up visits

Swollen joints count	Immediate Treatment, mean (SD)	Delayed Treatment, mean (SD)	p-value
Baseline	2.3 (2.8)	3.1 (3.6)	N/A
Visit 2	1.1 (1.7)	1.8 (2.5)	0.269
Visit 3	1.8 (2.9)	2.5 (3.9)	0.474

Two-sample t-test for the difference in the mean swollen joint count at each visit between the two treatment arms

5.6.4 Musculoskeletal ultrasonic assessments

The musculoskeletal ultrasonic assessments were performed as longitudinal images of greyscale (GS) and power Doppler (PD) of the following joints bilaterally:

- Inter-carpal (right and left)

- Radio-carpal (right and left)

- Ulnar-carpal (right and left)

- Metacarpal 1-5 (right and left)

In total 16 joints were assessed, generating an average of 74 images per patient, per visit. This accounted for a total number of 13.383 ultrasound images. The scoring system was described more in detail in the Methods chapter. Each joint was graded on a scale of severity of synovial inflammation from 0 to 3. Two different approaches for data analysis were developed:

1. For a general assessment: binary allocation of scoring: 0 (no visible sign of inflammation) and 1 (visible sign of inflammation) both in Greyscale and Power-Doppler.

2. For a more specific assessment: summary of all grading per patient per visit (minimum score = 0; maximum score= 16).

5.6.4.1 Binarised analysis in Power Doppler

The binarised mean score analysis in Power Doppler revealed a slightly higher score of inflammation for the patients in the Delayed Group at baseline. The only statistically significant difference was observed at six months follow-up as illustrated by Table 31 - Mean binarised Power Doppler ultrasound scores

Table 31 - Mean binarised Power Doppler ultrasound scores by treatment group at each visit

	Immediate Treatment, mean (SD)	Delayed Treatment, mean (SD)	p-value
Baseline	3.3 (4.0)	4.7 (4.9)	N/A
Visit 2	2.7 (4.1)	3.1 (3.4)	0.71
Visit 3	1.8 (1.8)	3.8 (4.2)	**0.04**

Two-sample t-test for the difference in the mean binarised Power Doppler ultrasound scores at each visit between the two treatment arms

Figure 9 - Binarised Power Doppler ultrasound scores
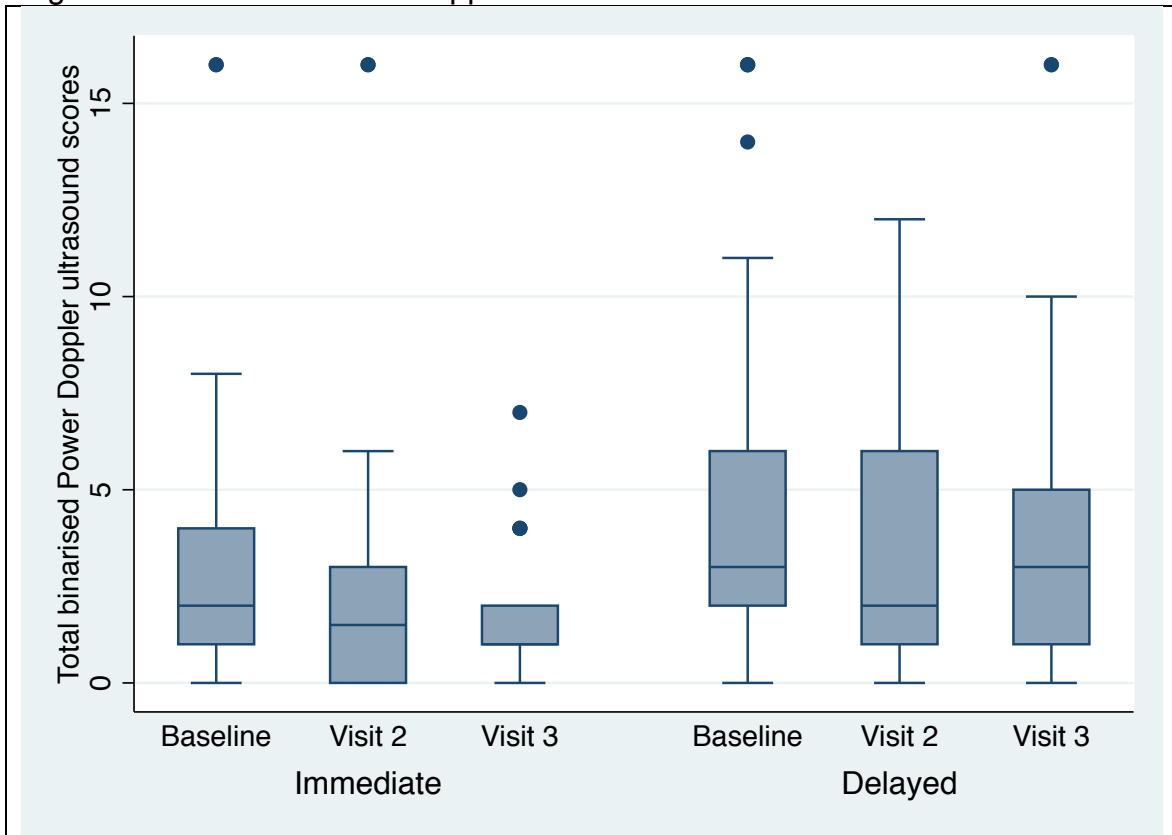
5.6.4.2 Binarised ultrasound analysis in grey scale

The binarised ultrasound mean scores in grey scale presented a higher value for the Delayed Treatment group at baseline compared to the Immediate Treatment group. There was no statistically significant difference between the groups at none of follow-up visits. This was presented in Table 32 - Mean binarised Gray Scale ultrasound scores

Table 32 - Mean binarised Gray Scale ultrasound scores by treatment group at each visit

	Immediate Treatment, mean (SD)	Delayed Treatment, mean (SD)	p-value
Baseline	5.8 (3.9)	6.6 (4.6)	N/A.
Visit 2	4.6 (4.1)	5.1 (3.4)	0.664
Visit 3	4.3 (2.5)	5.4 (4.1)	0.304

Two-sample t-test for the difference in the mean binarised Gray Scale ultrasound scores at each visit between the two treatment arms

Figure 10- Binarised Gray Scale ultrasound scores
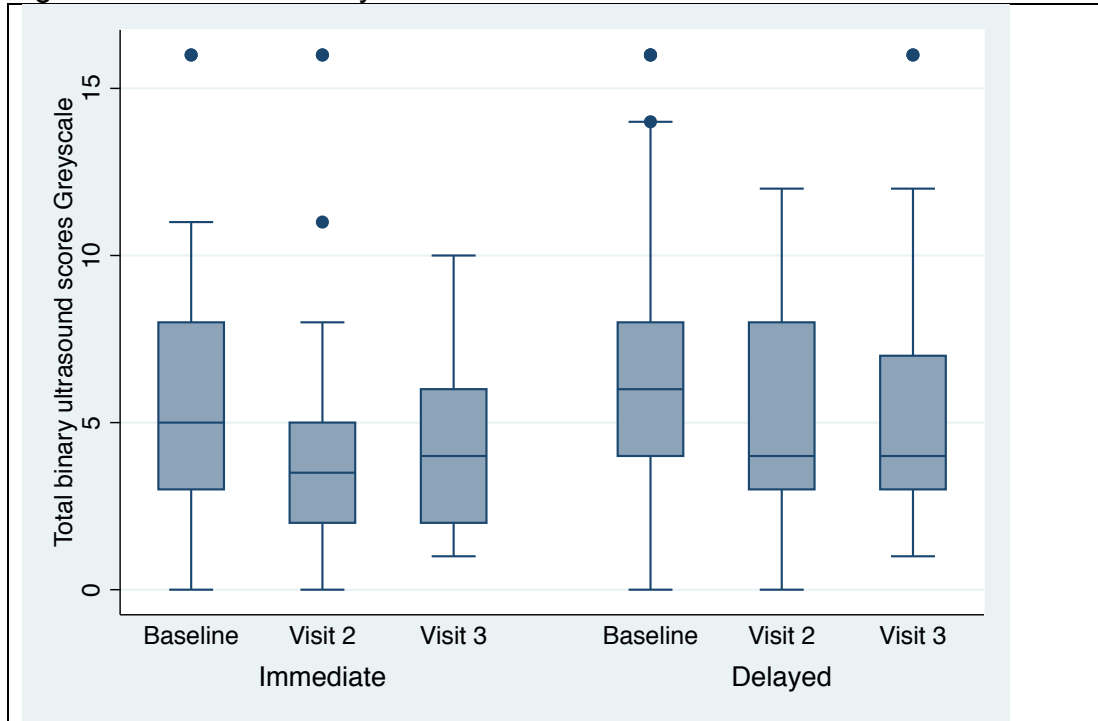
5.6.4.3 Summarized analysis – total scores in Power Doppler

The mean value of the total scores of inflamed joints in Power Doppler at baseline visit was higher in the Delayed Treatment group as presented in Table 33 and Figure 11. There was no statistically significant difference between the treatment arms at none of the follow-up visits.

Table 33 -Total Power Doppler ultrasound scores by treatment group at each visit

	Immediate Treatment, mean (SD)	Delayed Treatment, mean (SD)	p-value
Baseline	5.2 (5.6)	7.2 (8.4)	N/A
Visit 2	3.2 (3.5)	6.7 (8.2)	0.062
Visit 3	3.8 (4.4)	6.2 (6.1)	0.141

Two-sample t-test for the difference in the mean Total Power Doppler ultrasound scores at each visit between the two treatment arms

Figure 11 - Total Power Doppler ultrasound scores
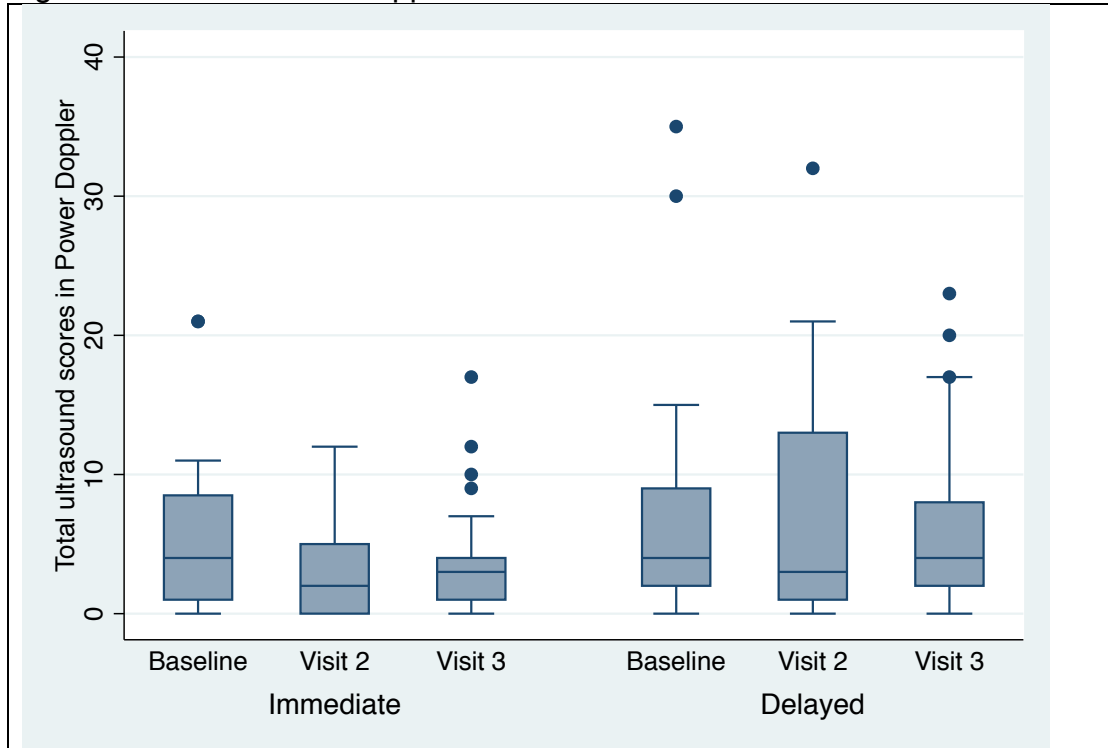
5.6.4.4 Summarized analysis – total scores in grey scale

The summarized analysis of the mean values for the grey scale ultrasound at Baseline presented a higher value in the Delayed Treatment group, compared to the Immediate Treatment group. None of the follow-up visits presented a statistically significant difference at none of the follow-up visits as illustrated by Table 34 and Figure 12

Table 34 - Total Gray Scale ultrasound scores by treatment group at each visit

	Immediate Treatment, mean (SD)	Delayed Treatment, mean (SD)	p-value
Baseline	10.0 (6.8)	12.1 (9.7)	N/A
Visit 2	7.0 (5.4)	10.8 (8.7)	0.073
Visit 3	9.4 (6.3)	10.2 (7.4)	0.603

Two-sample t-test for the difference in the mean Total Gray Scale ultrasound scores at each visit between the two treatment arms

Figure 12 - Total Gray Scale ultrasound scores
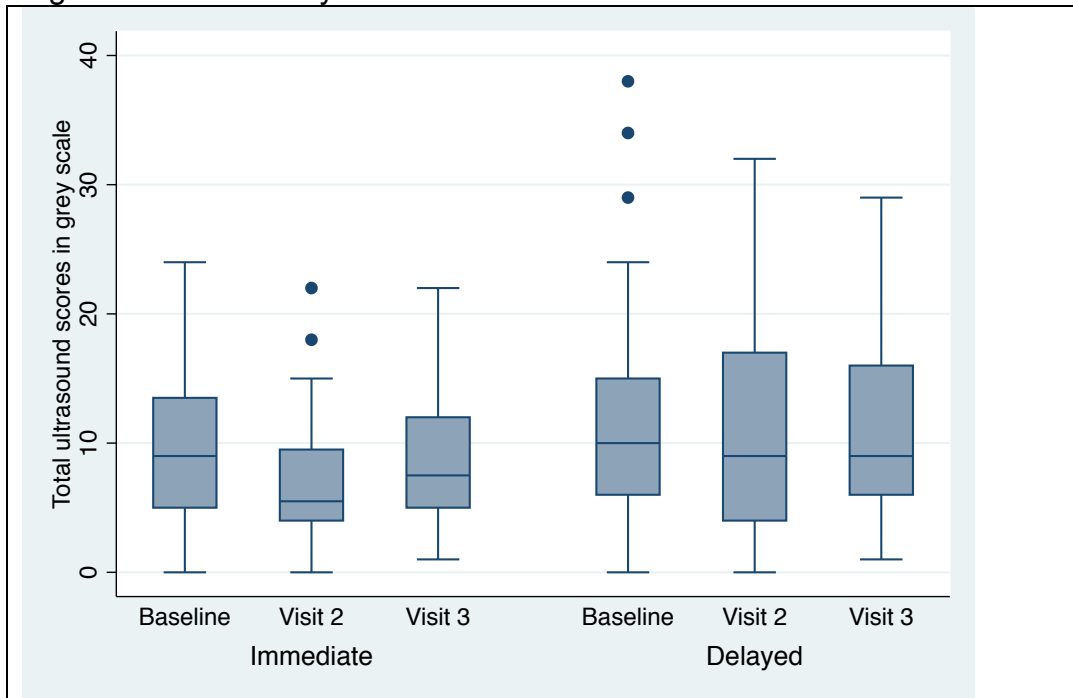
5.7 Medication changes

The most common medication groups used for the rheumatologic treatment of the patients from the OPERA cohort are presented in Table 35 for each treatment arm.

Table 35 – Description of classes of rheumatoid drugs for each visit by treatment group

	Immediate Treatment	Delayed Treatment	Total
Disease-modifying antirheumatic drugs (DMARDs) N (%)			
Baseline	11 (36.6)	17 (56.6)	28 (46.6)
Visit 2	9 (30.0)	13 (43.3)	22 (36.6)
Visit 3	9 (30.0)	14 (46.6)	23 (38.3)
Steroids			
Baseline	6 (20.0)	10 (33.3)	16 (26.6)
Visit 2	5 (16.6)	8 (26.6)	13 (21.6)
Visit 3	3 (10.0)	5 (16.6)	8 (13.3)
Nonsteroidal anti-inflammatory drugs (NSAIDs) N (%)			
Baseline	3 (10.0)	6 (20.0)	9 (15.0)
Visit 2	2 (6.6)	3 (10.0)	5 (8.3)
Visit 3	2 (6.6)	4 (13.3)	6 (10.0)
Biologics N (%)			
Baseline	10 (33.3)	10 (33.3)	20 (33.3)
Visit 2	10 (33.3)	8 (26.6)	18 (30.0)
Visit 3	8 (26.6)	6 (20.0)	14 (23.3)

The most common group of medications used in this cohort at Baseline was represented by DMARDs with a total of 28 (46.6%) of patients. Of these, 11 (36.6%) were in the Immediate Treatment group and 17 (56%) were in the Delayed Treatment group. At Visit 2 and Visit 3, there were 9 (30%) patients from the Immediate Treatment group. For Visit 2 there were 13 (43.3%) patients in the Delayed Treatment group and 14 (46.6%) for Visit 3.

Table 36 - Medication changes by treatment group at each visit

	Immediate Treatment	Delayed Treatment	p-value
Baseline – Visit 2 N (%)	5 (16.6)	6 (20.0)	p=0.940
Visit 2 – Visit 3 N (%)	4 (13.3)	6 (20.0)	p=0.571

Chi square test for the association between treatment arm and medication change

Some of the data regarding medication change was unavailable as described in section 5.5 Missing data. Based on the available data, Table 36 presents statistical tests for significance for change in medication between treatment arms.

5.8 Patient reported outcomes

5.8.1 EuroQuol

The EuroQuol (EQ-5D) questionnaire assessed five different dimensions of the patient's self-perceived health and well being with regards to different areas of life. Table 37 - EQ-5D mean scores by domains - is presenting the mean scores for each of these dimensions with the standard deviation between brackets for each treatment arm and visits.

The highest value for each of the first four dimensions was 3. This represented the lowest degree of autonomy and well being . The smallest value for each group was 1 and this represented the highest degree of autonomy and well being.

The fifth dimension represented a visual analogue scale (VAS) where the highest score represents the best state of self-perceived health. In a majority of the dimensions that addressed by this questionnaire, the Delayed Treatment group

presented slightly higher mean scores, however none of these was statistically significant.

Table 37 - EQ-5D mean scores by domains, mean (SD) by treatment group at each visit

	Mobility		Self-care		Pain/ Discomfort		Anxiety/ Depression		VAS	
	V2	V3	V2	V3	V2	V3	V2	V3	V2	V3
Gr 1	1.7 (0.4)	1.8 (0.4)	1.6 (0.6)	1.5 (0.6)	2.2 (0.5)	1.9 (0.4)	1.3 (0.4)	1.3 (0.5)	6.2 (2.2)	6.5 (2.1)
Gr 2	1.7 (0.4)	1.7 (0.4)	1.7 (0.5)	1.7 (0.5)	2.1 (0.5)	2.3 (0.5)	1.5 (0.5)	1.4 (0.5)	6.7 (2.0)	6.5 (2.1)
p-val.	0.717	0.626	0.613	0.231	0.154	0.132	0.286	0.573	0.443	0.949

Gr1 = Immediate treatment; Gr2 = Delayed treatment; V2 = Visit 2; V3= Visit 3
Two-sample t-test for the difference in the mean EQ-5D scores by domains at each visit between the two treatment arms

5.8.1.1 Mobility (1-3)

In terms of mobility the two treatment arms were relatively balanced at both follow-up visits with no statistically significant difference between the groups.

5.8.1.2 Self-care (1-3)

In terms of self-care the two treatment arms were relatively balanced. The Delayed treatment group presented a slightly higher value for both visits however this was not statistically significant.

5.8.1.3 Pain/ Discomfort (1-3)

The highest reported score for both treatment arms was noticed regarding pain and discomfort. In this case as well, the Delayed Treatment group presented a slightly higher mean score. This was not statistically significant.

5.8.1.4 Anxiety/ Depression (1-3)

In terms of anxiety and depression, both treatment groups presented the lowest mean scores from all the categories that were addressed. There was no statistically significant difference between the groups.

5.8.1.5 Visual analogue scale (VAS) (1-10)

The VAS scores were relatively balanced between both groups. The highest scores represented better self-perceived general health. There was no statistically significant difference between the groups.

5.8.1.6 Total EQ-5D Scores

Table 38 - Mean scores of the EQ-5D Questionnaire - presents the mean total scores of between the treatment arms from baseline to the follow-up visits. There was no statistically significant difference between the treatment groups in terms of mean scores from baseline to follow-up visits.

Table 38 - Mean scores of the EQ-5D Questionnaire, mean (SD) by treatment group at each visit

	Immediate Treatment	Delayed Treatment	P-value
Baseline	12.4 (2.8)	12.9 (2.6)	N/A
Visit 2	13.1 (2.9)	13.9 (3.1)	0.439
Visit 3	13.2 (2.5)	13.9 (2.5)	0.467

Two-sample t-test for the difference in the mean EQ-5D scores at each visit between the two treatment arms

5.8.2 Patient Health Questionnaire (PHQ-9)

The Patient Health Questionnaire (PHQ-9) is a depression test questionnaire.

The total scores represented: 0-6 = mild 6-10 = moderate 11-15 = moderately severe 16-20 = severe depression

Each question had 4 possible choices of answers. The answers were coded with zero being the least likely sign of depression and four being the most likely to present signs of depression.

The lower scores represented less evidence of signs of depression, while the higher scores could indicate potential signs of depression. These results however should be interpreted with caution. The purpose of presenting these results was to provide an overview of the data that was gathered through this study and not to provide a clinical diagnosis for depression of this patient population.

Overall, the patient scores pointed towards a higher mean score at baseline and a decreasing tendency of these values at the follow-up visits as presented in Table 39

Table 39 - Mean scores of the Patient Health Questionnaire (PHQ-9) mean (SD), by treatment group at each visit

	Immediate Treatment	Delayed Treatment	P-value
Baseline	11.4 (7.6)	10.8 (7.7)	N/A
Visit 2	9.1 (7.4)	8.6 (6.5)	0.846
Visit 3	7.7 (7.2)	8.1 (5.7)	0.895

Two-sample t-test for the difference in the mean PHQ-9 scores at each visit between the two treatment arms

In order to provide a deeper understanding of all the different dimensions that were analyzed throughout this questionnaire, the mean values for the scores for each dimension are presented in Table 40 PHQ-9 mean scores by domains and Table 41 - PHQ-9 mean scores by domains (continuation). The higher numbers represent worse outcomes.

Table 40 PHQ-9 mean scores by domains (1) by treatment group at each visit

	Anhedonia		Depressed mood		Sleep problems		Low energy		Appetite changes	
	V2	V3	V2	V3	V2	V3	V2	V3	V2	V3
Gr 1	0.9 (1.0)	0.5 (0.6)	0.8 (0.9)	0.5 (0.9)	1.5 (1.2)	1.0 (1.0)	1.6 (1.0)	1.2 (1.0)	1.0 (1.0)	0.7 (1.1)
Gr 2	1.2 (0.9)	0.7 (0.7)	0.8 (0.8)	0.7 (0.7)	1.2 (1.0)	1.1 (1.1)	1.5 (0.9)	1.2 (0.8)	0.7 (0.9)	0.7 (1.0)
P-val	0.327	0.443	1.000	0.461	0.418	0.694	0.727	0.988	0.306	0.903

Two-sample t-test for the difference in the mean PHQ-9 scores at each visit between the two treatment arms by domains

Table 41 - PHQ-9 mean scores by domains (continuation) by treatment group at each visit

	Low self-esteem		Concentration difficulties		Psychomotor agitation or retardation		Suicidal ideation	
	V2	V3	V2	V3	V2	V3	V2	V3
Immediate treatment	0.6 (0.9)	0.6 (1.2)	0.7 (1.0)	0.7 (1.0)	0.7 (1.0)	0.7 (1.0)	0.4 (0.8)	0.2 (0.6)
Delayed treatment	0.7 (0.8)	0.4 (0.6)	0.8 (0.9)	0.3 (0.7)	0.8 (0.9)	0.3 (0.7)	0.6 (1.1)	0.4 (0.9)
P-value	0.744	0.574	0.773	0.244	0.773	0.244	0.456	0.672

Two-sample t-test for the difference in the mean PHQ-9 scores at each visit between the two treatment arms by domains

5.8.2.1 Anhedonia and Depressed mood

Anhedonia is characterised as the lack of interest or pleasure in fulfilling activities that are normally considered enjoyable by the subject [115, 116]. As Table 40 illustrates, randomized patients from both treatment arms presented a slight decrease between follow-up visits with regards to these dimensions. This change however, was not statistically significant.

5.8.2.2 Sleep problems and low energy

The patients from this study provided the highest mean scores for these two dimensions. Considering the demographic characteristics of the participants, this result is in line with the scientific literature. As Table 40 presents, for both treatment groups, there was a decrease of this indicator over the follow-up visits but it was not statistically significant.

5.8.2.3 Appetite changes

This aspect did not present change in the Delayed treatment group and only a small decrease in the Immediate treatment group. None of these changes was statistically significant as described in Table 40.

5.8.2.4 Low self-esteem, Concentration difficulties and Psychomotor agitation or retardation

There was no change of the mean scores of these dimensions in the Immediate treatment group while the Delayed treatment group presented a decrease for all the three measures as presented in Table 41.

5.8.2.5 Suicidal ideation

Table 41 illustrates that both groups presented a decrease of this measure between the follow-up visits. This was, however, not statistically significant.

5.8.3 Oral Health Impact Profile (OHIP-14) baseline, 3 months, 6 months

The Oral Health Impact Profile (OHIP-14) is a self-administered questionnaire of 14 items classed in seven dimensions of health assessing the impact of oral health on the quality of life of the patient.

The higher scores mean worse self-assessed oral health status, meanwhile the lower scores mean a better self-assessed oral health. The patient's lowest score was 0 and the highest score was 48. Table 42 - Total scores of the OHIP-14 and Table 43 - Mean scores of the OHIP-14 by dimensions of health. None of the differences between groups was statistically significant.

Table 42 - Total scores of the OHIP-14

	Immediate Treatment	Delayed Treatment	P-value
Baseline	16.2 (13.3)	12.7 (10.6)	N/A
Visit 2	16.6 (15.0)	12.9 (11.9)	0.375
Visit 3	12.7 (14.4)	8.2 (9.3)	0.332

Table 43 - Mean scores of the OHIP-14 by dimensions of health

		Immediate Treatment	Delayed Treatment	P-value
Functional limitation	V2	1.1 (1.1)	0.7 (0.8)	0.282
	V3	0.4 (0.6)	0.3 (0.5)	0.951
Physical pain	V2	1.4 (1.1)	1.2 (1.0)	0.638
	V3	1.2 (1.0)	0.9 (0.9)	0.398
Psychological discomfort	V2	1.6 (1.4)	1.3 (1.1)	0.430
	V3	1.5 (1.4)	0.8 (0.8)	0.135
Physical disability	V2	1.7 (1.2)	0.8 (1.1)	0.326
	V3	0.8 (1.2)	0.5 (0.9)	0.507
Psychological disability	V2	1.3 (1.2)	1.2 (1.0)	0.699
	V3	1.0 (1.2)	0.6 (0.9)	0.394
Social disability	V2	0.7 (1.1)	0.6 (1.0)	0.755
	V3	0.6 (1.2)	0.2 (0.5)	0.311
Handicap	V2	0.8 (1.1)	0.7 (0.9)	0.630
	V3	0.6 (0.9)	0.3 (0.5)	0.252

5.8.3.1 Functional limitation (0-4)

As presented in Table 43 the area of functional limitation encompasses the first two questions of the OHIP-14 questionnaire and refers to the inability of a person to pronounce words or to sense taste. The Immediate treatment group presented a slightly higher mean score compared to the Delayed treatment group at Visit 2 and the two groups presented similar mean values at the follow-up Visit number 3. The change was not statistically significant.

5.8.3.2 Physical pain (0-4)

Physical pain was the third highest rated indicator by the patients, immediately after physical disability and physiological discomfort. This dimension refers to pain and discomfort localized in the oral cavity. Both groups presented a not statistically significant decrease of these mean values at follow-up visits. This can be observed in Table 43.

5.8.3.3 Psychological discomfort (0-4)

This dimension was the second highest rated by the patients. Self-consciousness and tensed state caused by oral health problems were the defining characteristics of this area of investigation. Neither of the two groups presented a statistically significant decrease between visits (please see Table 43).

5.8.3.4 Physical disability (0-4)

This was the highest rated dimension by the patients in the questionnaires as presented in Table 43. The questions relating to this field were describing episodes of inability to eat properly caused by functional impairment of the dentition. In this case as well, the Immediate treatment group presented a higher mean value, compared with the Delayed treatment group and both groups presented a decreasing tendency over visits which was not statistically significant.

5.8.3.5 Psychological disability (0-4)

The questions referring to psychological disability were related to patient's difficulties to relax and sense of embarrassment – both caused by oral health problems. The tendency, in this case as well, was decreasing between visits, with

slightly higher mean values for immediate treatment group. This can be seen in in Table 43.

5.8.3.6 Social disability (0-4)

This dimension aimed to assess the extent to which the patients' encountered difficulties in performing their daily activities or if they felt irritable with regards to their social interactions because of oral health problems. Both treatment groups presented a decreasing mean score between the follow-up visits that was not statistically significant (please see Table 43).

5.8.3.7 Handicap (0-4)

The last dimension of the Oral Health Impact Profile, presented in Table 43 explored the patients overall level of satisfaction and capacity to fulfill their tasks in relation to their oral health status. This domain as well, did not present a statistically significant decreasing tendency between the follow-up visits.

5.9 Results of the Qualitative Interviews

5.9.1 Overview

In the followings, the reader will be guided through the demographic characteristics of the study population and the results of the qualitative data analysis. The main themes that emerged from the discussions are related to the patients personal experiences regarding the way rheumatoid arthritis affected their quality of life, the role and place of oral health as a health priority and encouraging or hindering factors to take part in the clinical trial (Figure 15).

Some of themes that emerged from the discussions were difficult to set in clearly distinctive categories as these themes were crossing over several different topics. For example "Oral health" could be included both in "Periodontitis and oral health" as well as "Comorbidities and health priorities"

5.9.2 Demographics

The demographic characteristics of the patients who consented to take part in the qualitative interview process are presented in Table 44. The median age for the patient population was 60 [57,64], whilst the median number of years spent since they were diagnosed until the time of the interviews was 19 [12,25] years (Table 44).

Table 44- Demographics of the patient population (qualitative interviews)

Pt #	Gender	Age	Observations	Years since diagnosis
1	F	60	Randomized - delayed	19
2	M	86	Unconsented	20
3	F	83	Unconsented	60
4	F	37	Unconsented	9
5	M	52	Randomized - delayed	13
6	F	59	Unconsented	20
7	F	68	Unconsented	22
8	M	65	Randomized - delayed	30
9	F	60	Unconsented	67
10	F	65	Randomized - delayed	6
11	F	55	Randomized - immediate	12
12	F	59	Unconsented	2
13	M	54	Unconsented	14
14	M	64	Not eligible	10
15	F	62	Randomized - delayed	36
16	F	47	Randomized - delayed	15
17	F	61	Randomized - delayed	15
18	F	62	Randomized - immediate	25
19	F	62	Randomized - delayed	30
20	M	57	Randomized - immediate	20
21	F	57	Randomized - immediate	1
Median [IQR]		60 [57,64]		19 [12,25]

As can be seen in Table 44, there were 21 participants in the qualitative part of the research project. In term of gender representation, 15 participants were females and 6 were males.

Females had a higher proportion in the participant group as rheumatoid arthritis has a higher prevalence in females than males [117-119].

More than half of the participants (13) consented for periodontal screening in the study, while the remaining participants did not. The main objective of the qualitative component of this study was to provide a better understanding of the reasons why certain participants choose not to take part in this clinical trial.

Another major question was to understand how study participants feel about being in a control group and receiving a delayed treatment of their periodontal disease. Therefore, a large proportion of the randomized participants (67%) were in the delayed treatment group.

Figure 15 presents the main 3 categories of merging themes: RA and Quality of Life, Oral Health and The Study. Each of these main themes presented a number of sub-themes that evolved as the dynamics of the interviews progressed.

Figure 13 - Qualitative interview themes
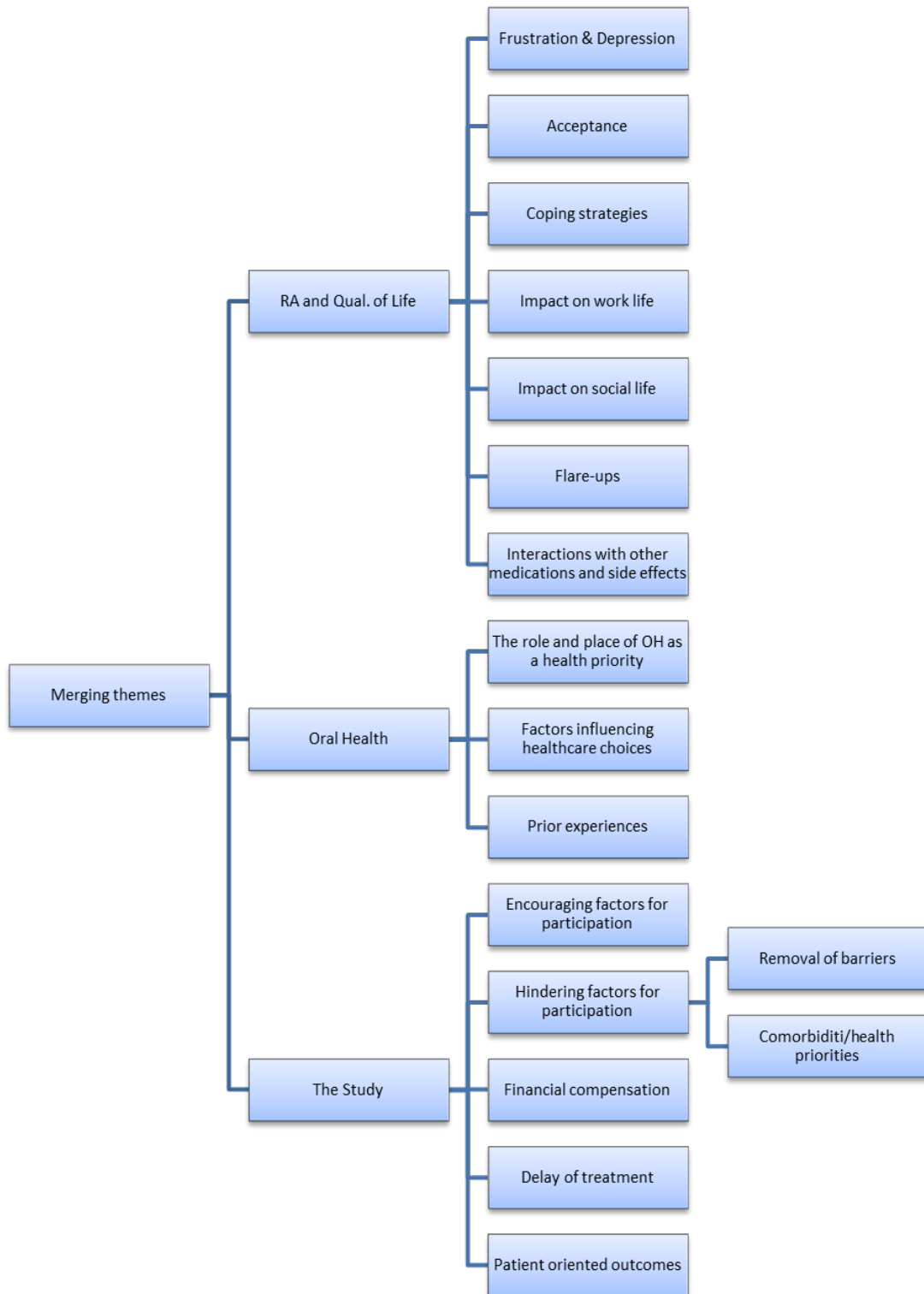
5.9.3 Results of the interviews

In the followings, the results of the interviews are presented together with the relevant quotes from the participants for each one of the topics.

Besides the initial topics, the main themes that emerged from the interviews were related to the effects of rheumatoid arthritis on the quality of life of the patients, their health priorities, the issues related to the delayed treatment of the control group, financial compensation and patient oriented outcomes of the study.

5.9.3.1 History of the condition

The first topic was represented by the history and onset of rheumatoid arthritis. The reason for this was to set the scene for the patients and to facilitate the recall of their experiences related to their condition, as well as the psychological impact of this experience.

The study participants were diagnosed on average 21 years ago with rheumatoid arthritis. Patient 3 was diagnosed 60 years ago and patient 21 was diagnosed 1 year ago. A number of participants described the onset of their condition as a very distressing moment, illustrated by the following statement:

> "I remember going to pick my son up from school and walking up
> high street and just with tears rolling down my face because
> I was in such pain and I am not a baby when it comes to pain, I
> think I have got quite a high pain threshold, but it was just I had
> never known anything like it and then it just got worse from there..."
> (PATIENT 1 p5)

> *"It started badly. It started with my shoulder and then it just gradually started to go to my hands and you know and physio wasn't helping." (PATIENT 11 p1)*

Several patients reported similar problems to Patient 1. They were feeling severe pain of unknown origin and were seeking out help from their general practitioner. Comments included:

> *"I got worse and worse and then I did sort of erm have an episode where I couldn't move, I couldn't get out of bed or anything and I managed to get a neighbour eventually." (PATIENT 17 p2)*

> *"I must have been suffering in agony because I was missing time from work and I was ringing them up." (PATIENT 20 p1)*

There was a very strong level of consensus amongst the participants in terms of the impact of the onset of rheumatoid arthritis has had on their lives. They describe experiencing severe pain, non-responsive to common analgesics that were available over the counter. The pain did not diminish in time in terms of intensity but it was getting gradually stronger and harder to resist, as follows:

> *"I do you remember the little girls used to wear long white socks, I couldn't put them on my children. That was a… big problem… Distressing and depressing." (PATIENT 3 p2)*

"Oh my God, what's happening to me". All I could move was my eyes, couldn't move anything else. I just went into a complete erm, I don't know what you would call it. It's like when I do get down the side, I do get where I lock where I go into really bad pain, I get a flare-up and I will lock all down the side." (PATIENT 1 p5)

The onset of rheumatoid arthritis was a highly traumatizing event for most of the participants both physically and emotionally. Sometimes it took a while until they received the correct diagnosis and medication and afterwards they had to learn to live with a chronic condition for the rest of their lives. The patients were unaware of their situation of being in an early phase of a chronic inflammatory condition and found themselves distressed with severe pain and trying to understand what this meant to them. Comments included:

"The children thought I was going to die. I heard them talking to my wife and er the er they said "Is dad going to die?" and I though, blimey, I must look bad, but I was so thin me bones were sticking out all over the place." (PATIENT 14 p2)

"I mean remember on more than one occasion getting stranded half way home with the buggy, I just couldn't walk any further, so I would have to stop for about fifteen, twenty minutes to try and build a bit of energy and wait for the pain to subside before I could carry on. So yeah, it was really restrictive." (PATIENT 5 p2)

"The difficulty I was facing whilst I was working was the inability to hold a pen properly ….. And work and a computer. Erm, sitting down

meant that my joints got really stiff, my knee joints and my back…
And my feet and as a consequence mobility as I say became very
bad… I couldn't get upstairs to the upstairs offices."
(PATIENT 10 p2)

"You know, where before I used to think nothing of it, I would go off and
do what I needed to do. Now, I can't do that, if I'm in pain I have
think right I can only do one shop today, or I can't walk that far
today." (PATIENT 12 p4)

In some of the cases, there was a delay in starting the correct treatment because
the symptoms were not recognized as specific for rheumatoid arthritis. This was
the case for several patients. Patient 12 reports that it went undiagnosed for nearly
18 months.

"I have had a lot of other treatments that haven't helped a great deal I
didn't respond, the blood tests showed that I didn't response very
well to those treatments that I was having. Until I can't think how
many years ago now, quite a few years now I have started on
infusion antiTNF infusion, which I take Rituximab."
(PATIENT 15 p1)

5.9.3.2 Rheumatoid arthritis and quality of life

Figure 14 – Theme: Rheumatoid arthritis and quality of life
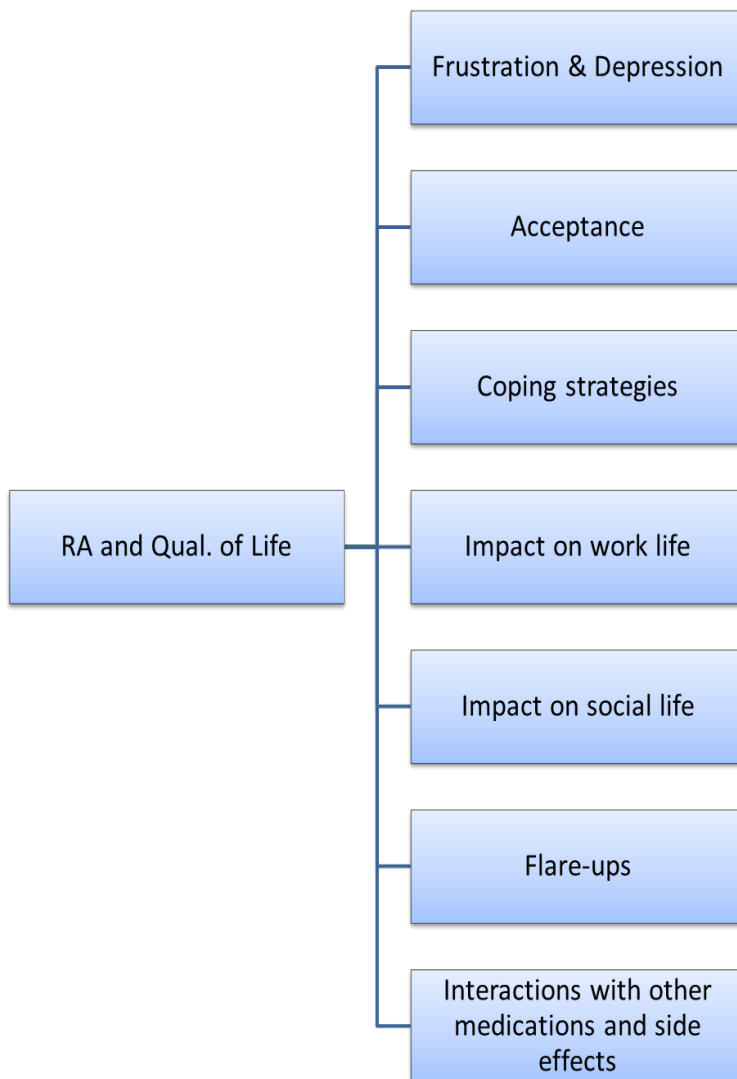
There were several similarities in the stories presented by the patients regarding the impact of rheumatoid arthritis on their quality of life. Having to learn to live with a chronic condition there was a common pattern in the stories presented by the

patients: in the beginning there is frustration and depression, which later will develop into acceptance and finally coping strategies. As a result, a number of sub-themes emerged from the discussions that described this shared experience of this group of patients.

The way the quality of life of patients suffering of rheumatoid arthritis is affected, seems to present a number of similar stages that are presented below.

The following sub-themes emerged:

- Frustration/Depression

- Acceptance

- Coping strategies

- Impact on work life

- Impact on social life

- Flare-ups

- Interactions with other medications and side effects

5.9.3.2.1 Frustration/Depression

Several participants described rheumatoid arthritis on their overall quality of life as having a strongly emotional, quite traumatizing impact. The onset of the condition was accompanied by feelings of frustration and even depression.

> *"Everyday things that I would have done without blinking an eye just became totally impossible to do because I had no grip in my hands, no strength then to actually get myself up in the bed."*
> *(PATIENT 1 p3)*

"So it can be frustrating, erm. If you know because people can't see it and "Oh yeah, you've got arthritis, well other people manage" but every person is different. You know, the arthritis, you know people deal with it differently." (PATIENT 12 p5)

As rheumatoid arthritis has a higher prevalence in females than in males, in case the patients were also mothers, they often developed feelings of frustration caused by the new barriers in parenting duties. These feelings augmented the general level of depression that accompanied the onset of severe, chronic pain.

"I do you remember the little girls used to wear long white socks, I couldn't put them on my children. That was a… big problem… Distressing and depressing." (PATIENT 3 p2)

"Cooking, cleaning, going out shopping, I don't go shopping anymore… Because I can't walk, so my husband does all this."
(PATIENT 19 p1)

Each patient is unique and reports a unique experience about the effects of rheumatoid arthritis on their quality of life. However, a common pattern can be found in all the stories they have related. These can refer to the sense of loss of utility in their family but also about the gratitude for the help that they received from their family members. *"Completely my life is changed. I can't do anything now, I have to rely on other people, my husband or my children. (PATIENT 19 p1)"*

Some of the patients are also mothers. They always tend to mention the impact that rheumatoid arthritis had on their life as parents. *"In the morning my joints are quite bad so I need help with things like getting dressed, my husband helps me in and out of the shower, even though we have an adapted bathroom he helps me in and out the shower in the mornings. I have a baby now so that together has a lot of complications I need help, you know, putting her in and out the highchair and feeding her." (PATIENT 4 p1)*

5.9.3.2.2 Acceptance

After the start of treatment and finding the correct dosage, the symptoms of rheumatoid arthritis diminished in most of the cases. The patients managed to learn to live with their condition. Patients reported that acceptance comes easier once the patients managed to discover new ways of doing things that they used to do before the onset of their condition.

> *"Because I've had the condition for so long I've learned to adapt but I would say it's changed my life and the career I would have pursued I haven't pursued now because of the problems with my arthritis and I have taken a job that it less, less, perhaps less intellectually demanding but it's less physically demanding so I haven't got the stress and I can, you know cope with that."* (PATIENT 4 p1)

> *"I have to accept that there is not a lot, you know, physically, I am not capable of doing an awful lot."* (PATIENT 1 p5)

"Because of the medication and also I find it difficult to erm, sit at any given time ….. I can't sit and I cant stand so I can't see what kind of job I can do as an engineer and I I managed to get about and do stuff, but I do have to erm sort of put my feet up quite a lot on the sofa, so I sit, I sit up..." (PATIENT 17 p2)

5.9.3.2.3 Coping strategies

From daily routine activities like personal hygiene, dressing up in the morning or driving a car, most of the patients had to develop new ways to learn how to live with their condition.

"I sort of use the palm of my hand when changing gear instead of holding with my fingers." (PATIENT 21 p3)

This topic has a crucial importance for understanding the patient's experiences with rheumatoid arthritis. Their personal experiences are shaping their priorities every day and these priorities are shaping their choices for healthcare.

"It has it has changed the way I have to live now because it rules what I do now." (PATIENT 12 p4)

"If I had to have teeth out, I have to have them out and that's the end of it." (PATIENT 4 p7)

Almost all the patients had to retire early or reduce their workload because of their diagnosis. This affected their socio-economic status, their independence and their

self-confidence as it was evidenced from this sample. Things that they were doing routinely on a daily basis became important challenges and some of them had to rely on the help of their family members and friends.

5.9.3.2.4 **Impact on work life**

Some patients are reporting the impact that rheumatoid arthritis had on their work life and socio-economic status was incredibly high. In some cases, this went as far as the patients had to change their living arrangements and make compromises in order to find ways to adapt to their new situation.

> *"I did retire early yes as a consequence and I had to give my home up because I couldn't get up the stairs any more… So within a very short space of time from 2010 to 2014 I retired early and I lost my home… I am living in a bungalow now, which has been adapted for my needs. I've got a wet room as opposed to a bathroom."* *(PATIENT 10 p3)*

> *"I was made redundant er in 2009 that was the second time, I was made redundant in in .. the year before as well erm and then I has another episode where I had to go into hospital and from then I have not really been able to sort of work…"* *(PATIENT 17 p2)*

Except for Patient 8 and Patient 14, all the other patients had to retire earlier or had to reduce their work schedule from full time to part-time because of the impact of rheumatoid arthritis on their work life. Patients reported that this had a major

negative impact on their socio-economic status. This is illustrated more in detail at the Financial compensation theme.

As rheumatoid arthritis does not always present visible signs, some patients were facing difficulties explaining what they are going through and why their condition impairs their ability to work.

> *"This is it, it's very hard to make people understand. Obviously people like job centres and people like that, if they can't actually see your illness... you know, it's awful to say but sometimes they might think that your swinging it or you're… Because if you've got a cut on your head, they can see that you've cut your head, but with arthritis because they can't see it. And you look healthy, they think "Well you're alright". But they don't see the pain that you suffer inside." it can be really frustrating. (PATIENT 12 p4)*

Some patients report that they had to attend several medical appointments for consultation and treatment and this made it for them difficult to continue working. As a consequence they had to retire early which represented an economic burden both for the individual and the society.

> *"I had to take early retirement from work and the first few years my knees were very swollen and very painful and my joints became and there was a time when because of the swelling and the fluid on my knees, I had to have quite a bit of fluid withdrawn and steroid injections as well, walking, a few years back was very slow and very painful and I still have the walking stick. Well I don't use it*

now, but there was a time when I had to use the aid of the walking stick…" (PATIENT 15 p1)

5.9.3.2.5 Impact on social life

Besides work, rheumatoid arthritis affected also the ability of the patients to enjoy their hobbies and social activities. The pain and swelling made it difficult for them to visit their friends and family members. Some patients reported that they enjoyed gardening or swimming and that they had to stop also these activities, because of their condition.

"It was just before my fortieth birthday. I was considering starting to play football for the veterans and do my first marathon, so it was quite a sad year for me really." (PATIENT 5 p1)

Patients are remembering their leisure activities often nostalgically and relate stories of regret caused by the barriers imposed by their condition to further enjoy these hobbies. As the patients work life was affected by their condition, they would be able to enjoy more leisure time but this is not the case, because the disease also affected their leisure activities.

"I used to enjoy football, fishing, things like that. I couldn't go fishing cos I couldn't hold the rod any longer in that one position holding the rod." (PATIENT 20 p2)

Sometimes, patients reported feelings of isolation because of their condition. Loneliness at advanced age can have a major impact on people's mental health.

> "Oh yes, I mean I would have worked til I was a hundred I think if I hadn't of been unwell. I love my job. I love the interaction with people, but the rheumatoid arthritis…..Prevented that. I don't do the walking. Erm, socially I've become a tiny bit isolated... Because I'm not with work colleagues anymore. I am not meeting people so there isn't structure to my life so it's, the impact has been quite profound." (PATIENT 10 p4)

5.9.3.2.6 **Flare-ups**

One of the other factors that were reported by the patients as difficult to cope with in terms of the impact of rheumatoid arthritis was the number and intensity of flare-ups. Comments included:

> "Yeah, I need longer in the morning, erm, I need a bit of time to warm up as well, because it is quite stiff in the mornings, my hands and feet particularly and you just have really strange like shocks and things like that. Last night was a really strange one, erm, I woke up in the middle of the night and I had the most severe pain in my knee I had had, I have had in years. It lasted for about twenty minutes and then it was totally gone. I thought when I get up this morning I am not going to be able to walk, the knee is going to be really painful, but nothing." (PATIENT 7 p3)

> "And I was rushed into hospital for a week and I have had some sort of, they don't really know what happened, but it was a massive,

massive flare-up. And I was poorly and that's happened to me twice." (PATIENT 17 p4)

"The first proper flare-up was pretty bad, yeah and for about, for about two years afterwards. I was really lucky because within six months I was given a biological drug, but there was all the other stuff like Methotrexate and quite a lot of other medications …. Steroids I was taking at the time as well, but yeah it is quite restrictive. My children were really young at the time as well. My son was three coming on four and my daughter was erm just two so …and my partner working full time at that time. So yeah it was quite restrictive, especially when I was trying to take the kids out shopping and things." (PATIENT 1 p5)

5.9.3.2.7 Medications and side effects

As patients can sometimes have other comorbidities, regardless if it's an acute or chronic condition, they always have to balance the new medication with the potential interactions and side effects that this has with their existing arthritis medication. Also, some patients sometimes report about the side effects of the medications that they are taking for controlling the symptoms caused by rheumatoid arthritis .

"They put me on Methotrexate, and gradually increased the dose until it had some effect. I was on 25 mg a week, which I think is the top dose that they can give me, erm so I was on that for about four years and then I had … for some reason I had a very bad reaction to it, and I couldn't keep anything down or in, you know I was either

being sick or diarrhoea with it, so they … I stopped the tablet."
(PATIENT 14 p2)

5.9.3.3 Periodontitis and oral health

Figure 15 – Theme: Periodontitis and oral health
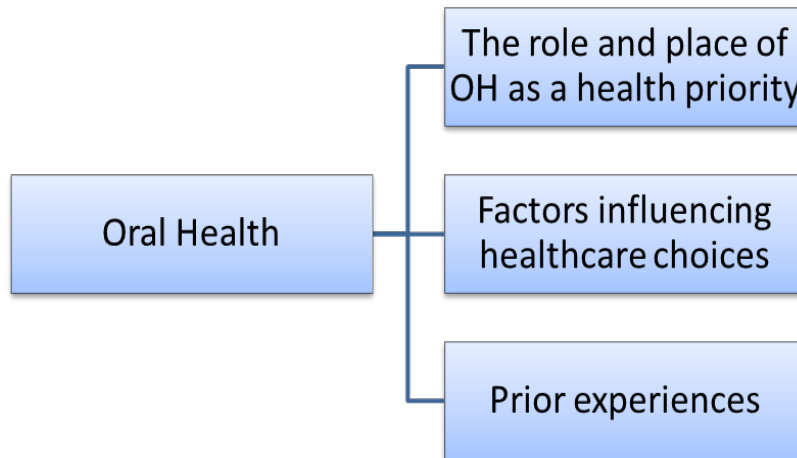
Patients discussed their oral health status, perceptions about oral health and previous experience that they had with dental care professionals. Few participants self-reported having a good oral health status, despite the fact that most of them self-reported having good oral hygiene habits: most of them reported about brushing their teeth twice a day. This however, was not possible on the days when they had a flare-up of their arthritis. As illustrated by:

> *"Right, when, if I have a bad flare-up of arthritis, I can't … and I miss it and I am not able, I don't have the strength to hold a erm my electric toothbrush, because it is quite heavy compared to a manual, so I have to go to a manual toothbrush just temporarily."*
> *(PATIENT 9 p5)*

"Erm, yes, if my shoulder hurts then it's it can be a bit difficult to brush."
(PATIENT 13 p4)

(Regarding brushing while having a flare-up) "Oh no, no, it's er very awkward to hold and brush my teeth." (PATIENT 18 p7)

A large number of participants reported to be unable to use dental floss because of the difficulties they encountered in grabbing small objects. Some of the patients in a more advanced age reported about experiences from their youth, with dental care professionals that were not the most positive. These past experiences influenced to some degree their attitudes and behaviours towards oral health in general and dental care professionals in particular.

"I will be honest I do need to see a dentist, because I have got gum disease. And my gums are receding and I do need to, I do seriously need to have treatment. But I am that frightened the fear is taking over me going to see a dentist. I just can't do it."
(PATIENT 12 p8)

The past experiences that the patients were reporting shaped their perception regarding oral health. However, patients acknowledge the importance of good oral health and they try to help their children to prevent the occurrence of oral conditions.

"Then you never used to go to the dentist, they used to come round the school, this is going back a long time nineteen fifties and sixties. … And then most of the time they just pulled your teeth out (laughs).

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That was, they never did any fillings or anything they just looked at your teeth and if they didn't like the look of it, they just pulled out your teeth. They were sort of your your initial teeth anyway not your adult ones, but that was all you would see was rows and rows of children sitting with things in their mouth where they had had teeth pulled out, but that was quite good really because that was the only time that people looking at your teeth because your, my parents and I think most parents at the age didn't bother with the children ('s oral health) …. My wife was had, used to have terrible problems with the fear of going to the dentist, but now she is she is much better… Whereas I think a lot of people don't go because they are frightened of something that has either happened in the past, or something they think is going to happen."
(PATIENT 14 p5)

"Yeah, I, I think I woke up under the gas. And er, I was there was blood all over the place and I was only about this high. At school. And I never went again. I stopped going for a long time."
(PATIENT 20 p7)

"I did when I was younger. Yeah, I did. I was I think about, I don't know, about 17 and I used to go to a dentist in ▮▮▮ way. That I can remember vaguely from when I was little and he was quite abrupt and rough. And I think that's right from the beginning that I was scared of a dentist really. You know, there was no "Oh tell when to stop if I'm hurting" or anything like that. It was just "Open your mouth and let's get on with it." (PATIENT 21 p5)

Participants mentioned the importance of developing a relationship based on trust with their dental care provider. This plays an important role on their attitudes towards oral health and their behaviours in seeking oral health care services.

"It was quite bad before I came to you. My gums were always inflamed and bleeding. But really and truly I didn't get that much help from my dentist. It was always just really antibiotics. You know to the point where I didn't have a lot of faith in them." (PATIENT 21 p4)

Patient 2 reports being afraid of needles and consequently being afraid of dentists. Teeth are not so important to him anymore and he would rather choose to have them all extracted instead of restorative treatments, in case it is needed.

"If I'm in pain I get there, it's the thought of the needle. The needle, yeah… When inquired about his preference for restorative treatment or extraction: "I suppose out would be the best at my age I suppose out, you know." (PATIENT 2 p5)

Another factor that needed to be addressed is represented by the comorbidities of the participants. Having multiple chronic health problems. This was further developed in paragraph 5.9.3.8 Comorbidities, health priorities.

Some patients reported that the medication they take for rheumatoid arthritis might have had negative side effects towards their oral health.

"I don't know if that drug would make you a bit more prone to the inflammation of the gums, but since I have stopped that and I have

gone on a different one, they have calmed down…. "When I was on Rituximab, I would have a terrible lot, I had only got to eat anything and mouth had got blood in it." (PATIENT 6 p2)

The participants also mentioned the oral health services delivery system as important. Patients consider that dental treatments in a private setting are more thorough and better quality, compared to dental care supported only by the NHS.

"He, it's a private practice... And I would love him not to be, but because of the time and the care and attention I get … It is quite noticeable. How much more time I can take doing things and him explaining things to me and the precision with which he makes my false teeth and how he puts new ones on when I lose another one that I wouldn't, if I could find a national health dentist that gave me that much time and care…" (PATIENT 9 p5)

Other patients shared this opinion as well. They believe that the quality of care in a private setting is superior compared to publicly fund dental services.

"I have had to change from a private dental care to a NHS dental care and I am not saying that there is any difference but I found that the speed with which the NHS dental hygienist did their work was in my opinion it wasn't as thorough as when I was paying for it privately… And erm, I wasn't sort of getting the feedback where I would have with the hygienist before... Where I have been asked certain questions there just didn't seem to be the time with the NHS." (PATIENT 10 p5)

Having to live with a chronic condition already, some patients reported the importance of having a sense of control over their own bodies and over their own health.

> "Yeah, because when your rheumatoid is bad you know about it, you can't do anything and when my ITP is bad. I'm having to control nose bleeds all the time and dental health if it's not causing you a problem it's like, it's a bit like the osteoporosis that I don't know it's there. I know it's something I need to be aware of but because it's managed with a calcium tablets and, you know, and everything else I don't need to you know I'm dealing with it I'm controlling it and I have to. My priorities are things that aren't so controllable. My dental health as far as I'm concerned is controlled, I'm controlling it." (PATIENT 4 p7)

When participants were asked about the way they feel regarding their oral health, and how they regard the visit to their dentist patients reported mainly using negative attitudes towards these experiences:

> "I suppose out would be the best at my age I suppose out, you know." PATIENT 2 p3)

> "It wouldn't be my favourite day out you know." (PATIENT 3 p4)

> "If I had to have teeth out, I have to have them out and that's the end of it." (PATIENT 4 p7)

These were mainly the attitudes of the patients that were more elderly. Younger patients reported that they would prefer to keep their natural teeth and have them treated.

> *So yes, I did give them a nice brush this morning before I came though, but it is easy I think to erm to, you can brush your teeth, but if you don't er try and keep your gums healthy as well the your teeth will eventually just fall out anyway, so you need to keep the two stuck together so there." (PATIENT 14 p11)*

> *Because I wouldn't like to lose my teeth. I mean until this time." (PATIENT 15 p9)*

5.9.3.4 The study

Figure 16 – Theme: The study
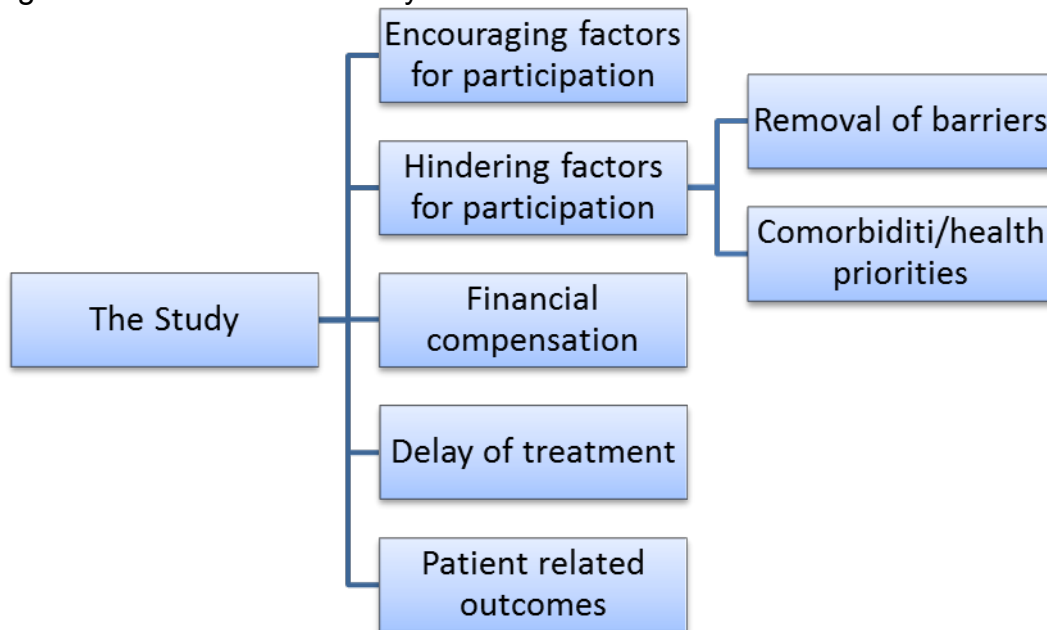
5.9.3.4.1 **Satisfaction about the study and reasons for taking part**

Most of the participants who consented to take part in the study considered it being a positive experience overall. They reported that the project was a good opportunity for them to become aware of their oral health status, specifically in terms of periodontitis.

"I'm really pleased actually that erm doing this study because erm had it not been for that, this could have gone on and on and it might have got to a really bad situation with my gums and I wouldn't have known so I am really pleased." (PATIENT 11 p2)

The professionalism of the research team was considered being very positive experience for the participants.

"Yeah, they have been good, I think the experience has been good. You staff have been really helpful and I am aware of what is happening every time I come and see you.   The hygienist was great, she explained what she was going to do and what she expected to do in future, so I think it has been a really good experience as well and eye opening as well." (PATIENT 5 p4)

Several consented patients that were randomized to one of the treatment arms expressed their special gratitude for the high quality of care that they received from the hygienist assigned for this project.

"She made me feel so comfortable and it's embarrassing as well when you go to dentist... I find I get embarrassed. And because of the state of my teeth. I didn't feel at bit like that from the moment I met the hygienist and I felt quite confident that she was confident. She knew what she was doing. She explained everything. And she told me if anything hurt or to stop, to stop her. I just felt so comfortable with her." (PATIENT 21 p7)

The patients reported that they felt appreciated and treated with respect during their visits at the Dental Hospital. They related stories enthusiastically about each step that they took during their trial participation, regarding both their research visits and treatment appointments.

> *"They were very inform informative and very kind... And they answered any questions I had and you yourself reassured me and made everything perfectly erm plain to me what I was undertaking and why I was undertaking... The significance of the tests so I found all of that to be very beneficial, yeah, very courteous, very kind, not a problem at all and I came away with a raised awareness... From being with the hygienist and she showed me how to use the interdental brushes or the floss whichever I preferred and a different way of maybe tackling the problem areas."*
> *(PATIENT 10 p7)*

Some of the patients were reporting with enthusiasm about their experience at the screening visit. This was a new type of experience and the patients quite positive about the process. However, some aspects of the screening visit that were considered exciting by some participants, were less pleasant for others. The negative experiences are described in the following chapter.

"Excellent, very, very professional… every step of the er the examination that they did they explained in detail before they did it and showed me all the different things that they were going to use, the instruments they were going to use and then when they going to do the saliva tests they showed me you know, all the equipment and everything they were going to use they showed me, so very good." (PATIENT 14 p6)

The screening process triggered the curiosity of some participants and with this occasion they also requested follow-up information about the results of the study.

"Well I find it very interesting, especially with the collecting of the saliva I would like to know what that entails. Erm. the plaque from my teeth and erm the blood tests what all the the connections with all those tests the findings how it erm." (PATIENT 15 p4)

Through this interview process we aimed to gather information about the views and personal values of each participant. Since every participant is unique, his or her priorities and motivations might be quite different. However, this being a relatively heterogeneous group in terms of age, gender as a consequence of their chronic condition a certain number of common denominators were extracted from these interviews, reflecting factors that they considered to be encouraging for their study participation.

A large number of participants reported that their main reason to take part in the trial was altruism. More specifically, they were hoping that by their participation they could help future patients to avoid the same amount of pain and suffering that they went through themselves.

"The purpose of my agreeing to this study is erm any type of study with regards to improvements in future developments for people with rheumatoid arthritis and gum disease… People in the future …hopefully won't so that won't have to suffer hopefully quite as much." (PATIENT 10 p7)

This opinion was shared by most of the participants. Altruism towards fellow patients seems to be an important motivational incentive for patients suffering with rheumatoid arthritis.

"So yeah you know anything that is going to help or or help people in the future in going to be better really." (PATIENT 17 p6)

However, some participants considered that this trial, being offered at the Dental Hospital, will make them benefit of a good oral care without significant effort, and in the same time they reported a certain level of curiosity about the results.

"No, that's, that's one of the reasons I joined this study was also a selfish reason. The appointments are there. I can come and see a dentist, I can just come and see a hygienist and you know that's great for me. Whereas with my own dentist, it's left to me to go and do the footwork then, if it was left to me, I wouldn't do it, so this is quite good for me and as I say, it is a bit selfish, but . "I mean that has always been one of the main reasons I have taken part in trials , I have taken part in quite a few and one of the main reasons is always to find out what the outcome is and what you and I have learnt from it. That is why it has always been of interest to me." (PATIENT 5 p7)

Patient 13 refused to consent for screening unless he was guaranteed to receive complete and free of charge dental treatment for all his oral health problems. Some patients recommended financial compensation as a potential incentive to increase the level of interest of the potential participants of the trial.

> *"And perhaps compensating patients financially for taking part is important because for me it's not such a big thing but for some people, you know, they do incur costs and you know some people are carers you know or you know for me child if if I could pay somebody to look after my child rather than asking a favour you know it would be more feasible. I would look into it as to how much time it was and whether I was being compensated for that in any way. Because, if it was, let's say, let's say for example it was 2 hours a month for 5 years and I wasn't getting anything for it. I was just doing it, I was just doing it for the, you know, I'd I'd look in, you know, I'd look into it."* (PATIENT 4 p7)

A few patients were involved in other clinical trials before. This was a positive experience for them; therefore they decided to participate in our study as well. Some patients expressed their desire to participate but the logistics of getting to the Dental Hospital were too difficult for them to manage. Therefore arranging transportation to the Dental Hospital helped significantly their willingness to participate in the study. This was the case for Patient 4 and Patient 7.

A few participants expressed their interest in finding out the results of the study and mentioned this also as an incentive for their participation.

Some patients believed that it would have been easier if they would have been invited to participate in the trial by the clinician from the rheumatology clinic.

"I think that my rheumatologist should have sort of, they don't tell you to be sort of extra special careful with your teeth and I think they should." (PATIENT 17 p4)

5.9.3.4.2 Dissatisfaction about the study and barriers for study participation

Providing an accurate and potentially negative feedback seemed to be one of the most challenging parts of the interview process due to potential cultural bias. Certain groups of patients seem to find it easier to provide positive feedback than criticism about their experiences in a study. This finding can be also linked to the CONSORT statement presented in the previous chapter where it has been demonstrated that one third of the patients consented to take part in the study but never attended their screening visit. The patients were encouraged to provide genuine feedback about anything that they felt that could have been done better. In certain instances, the patients were asked to imagine that they would be running the project and to try to suggest what things they would do differently.

The patients overall did not report any major negative experiences regarding their participation in the study however, a few issues did emerge, for example the saliva sampling process, which was described by one of the patients as follows:

"a little awkward and embarrassing." (PATIENT 1 p5)

Furthermore, periodontal probing was reported to be unpleasant by one of the participants. Other participants shared this opinion, but they all reported that they expected this to be the situation and it did not represent a major problem for them.

"The only thing that I dislike but I cope well with is when you put the little and you are measuring the depth of the gums?" (PATIENT 15 p4)

It was important to explore the reasons why some patients would be reluctant to participate in the study in order to better understand their perceptions and if there are potentially barriers that could be removed by the research team. A large number of patients reported having negative experiences with dentists in the past and this discouraged them to participate in our trial.

"Well I am concerned that my dentist hasn't done what needed to be done to save my teeth from breaking." (PATIENT 13 p4)

The location of the Dental Hospital was mentioned as a hindering factor by several patients.

That was because it was the Dental Hospital and I find it difficult to get from my part of the town to the Dental Hospital." (PATIENT 2 p5)

This opinion was shared by a number of different patients. Due to classic signs and symptoms of rheumatoid arthritis like mobility problems, fatigue, morning stiffness and logistic issues with the traffic from their homes to the city centre, they found that without help, they could not attend their research appointments.

"It is a bit far away, you know the other side of town but they are moving to a new hospital shortly which will be more accessible, yes." (PATIENT 18 p3)

Besides the location of the Dental Hospital, patients mentioned forgetfulness and overlap with other medical appointments for rheumatology clinic or for other comorbidities as being important hindering factors for study participation.

"I completely forgot." (PATIENT 3 p5)

Patient's comorbidities that lead to other hospital appointments were also mentioned by a number of patients as being a reason not to participate.

"But the other thing to remember is for patients like me who have got rheumatoid, they've probably got other going ongoing conditions as well. There is so many things you have to try and focus on." (PATIENT 4 p6)

This opinion was shared by several patients as a hindering factor for their study participation.

"No, no I probably haven't been to the dentist, it has got to be a year now, so but part of that is that I have so many appointments for different things at the moment, that unless I am reminded of an appointment, or given an appointment they tend to slip away." (PATIENT 5 p6)

5.9.3.5 Financial compensation

This topic was also a new theme that emerged from the interviews and was added to the final topic guide. It was reported being important by some patients and less important by other patients.

A few patients mentioned that financial compensation could be a fair and reasonable stimulus to participate in the study.

> *"That always seems to help I did a lot of groups and the financial side of it isn't a big thing to me. When I did the conferences it was all about expenses I was happy for my expenses to be paid, but a lot of the groups I also did erm, it would be like an interview, but there would be ten of us and we would sit around and the discussion would be recorded and you usually found that all those groups would be full because people were getting financial….. they were being paid for it basically, but you would find that they were all full, all of them." (PATIENT 5 p7)*

5.9.3.5.1 Removal of barriers

This topic was composed of suggestions and feedback from the patients perspectives about the solutions that could be arranged by the research team in order to facilitate patients study participation. Some of these hindering factors were addressed by the research team, as the project was going on: patients received phone call reminders about their appointments and those patients that required assistance for getting to the Dental Hospital, received support in arranging the logistics around getting to their appointments.

"Because as I say I wouldn't have been able to undertake the study unless I'd have had payment for transportation." (PATIENT 10 p10)

Financial incentives were set in place to compensate for the loss of time and logistics for the research and treatment visits. As all patients are unique and so is their situation, some patients did not feel that financial incentives should encourage patients study participation.

"I never give it a thought, no, no. Well you go for yourself really don't you so I don't think money or that would be you know .... Yeah... I always think if you are suffering and if you think you can find an easier way to help yourself, that's what I would do."
(PATIENT 6 p7)

Some patients that reported to suffer of dental anxiety suggested that the only way they would participate in the study would be if the screening and treatment would be done under general anaesthesia.

"I mean I did say to my son because he keeps telling me off he says, "Mom, you really need to go and get your teeth sorted… And I said, I will go if they can put me to sleep" (laughs). If they can knock me out …. Yeah. I said that's the only way I would have it done."
(PATIENT 12 p9)

5.9.3.6 Delayed treatment

This topic was one of the new topics that emerged as a result of the interviews. It was important to understand the feelings and perceptions of the patients about the topic of being in the delayed treatment group and how this would affect their study participation and adherence to the study protocol.

Regarding the topic of being in the delayed treatment group, most of the participants expressed their desire of being treated as soon as possible after diagnosis.

The opinions regarding the delay of treatment range from some patients considering that there should be no delay at all:

"I think it should be done straightaway." (PATIENT 6 p6)

To patients that believe that six months is a reasonable waiting time:

"6 months would be reasonable for the delay of the treatment in the control group." (PATIENT 2 p8)

To some patients agreeing in theory to go as far as 18 months of delay.

"I am not really fussed. I will leave that for the experts, but personally I would say eighteen months would probably be you know, but I agreed to take part in the trials, so you know so I agreed to take

> *part in the timescale as well, which I am quite happy to do."*
> *(PATIENT 5 p5)*

However, the upper threshold of most patients seem to go towards six months delay of treatment. The delay is easier to accept to participants that expressed a great level of confidence in the research team.

> *"I was hoping not to be in the delayed group, but as I am in the delayed group then I leave it to you to help me as best you can."*
> *(PATIENT 15 p6)*

This idea is reflected in the opinion of other participants as well, but consider the easiest acceptable waiting time being six months.

> *I would have preferred to have been into the first group… So I don't think there is a problem because you are looking after me. I mean I was just a little bit worried because if there was an abscess or something like that, but I hadn't and there was no decay it was just sort of like the receding gums that were causing the problems… So I wouldn't want to go any longer than that because erm you know a lot can happen in six months can't it?" (PATIENT 17 p6)*

In case of a longer delay, some of the participants reported that they would seek help outside the trial.

5.9.3.7 Interview notes about participants

This topic was reserved for any comments or observations made by the interviewer regarding factors that might play be playing a role in the interpretation of the results from the interviews. For example this could be the body language of the participants, anything unusual that can be observed and noted by the interviewer.

Some of the patients, were trying to show a strong and independent attitude. They sometimes had very short answers, often only one-word answers, and it was very difficult to stimulate them to elaborate on their thoughts.

When speaking about the onset of rheumatoid arthritis and the impact of the disease on their quality of life, some patients answered along the line of:

"I didn't stay in and weep and mope." (PATIENT 3 p2)

The same patient who reported that has no difficulties in gripping small objects like a toothbrush because of the join deformities, however at the end of the interview, the patient struggled to grip the door handle to open the door.

One of the respondents was actively involved in the National Rheumatoid Arthritis Society as a patient's representative (Patient 5).

Some of the stories related by the patients carry very high emotional charge and the way patients relate about the impact that rheumatoid arthritis had on their quality of life are sometimes very sensitive topics. One of the patients had to give up her home and work as a consequence of her condition (Patient 10).

One patient conditioned study participation by receiving free dental care for other, non-periodontal oral health problems (Patient 13).

5.9.3.8 Comorbidities, health priorities

As the average age of the participants is around sixty years of age, some of them might be suffering from comorbidities. In order to get a better insight in the reasons why they might or might not participate in the study, it was considered important to understand their healthcare priorities and the impact their comorbidities have on their life and as a consequence on their healthcare choices. Another factor was to understand where is oral health situated on their list of healthcare priorities.

Although several patients declared oral health as a main priority in the beginning of the interview, as the discussions evolved and they reported on comorbidities, they presented a tendency to prioritise other comorbidities compared to oral health.

> *"So I have rheumatoid arthritis and I have asthma/COPD, so I have breathing problems, but again somebody at the QE is looking after me there, so they are helping me with that. And that is linked to what used to be a constant round of chest infections, but they now seem to have this under control and then oral health is the third most important thing in my life." (PATIENT 9 p5)*

As most of the patients have multiple comorbidities, they tend to place oral health as the last one on the scale of importance: vascular disease, rheumatoid arthritis,

Chron's disease, asthma, chronic obstructive pulmonary disease (COPD), diabetes, high blood pressure.

> *"I think, erm, probably the second most important oral health, because I don't think that oral health is taken into consideration of other that can cause other health problems…" (PATIENT 15 p2)*

These health priorities have to take into consideration the age of the participants, their level of health literacy, socio-economic status and length of time since they have been diagnosed with rheumatoid arthritis.

> *"My chest really, my chest is first then my rheumatoid. My teeth, round about third I think to be honest." (PATIENT 7 p2)*

One participant mentioned a list of five comorbidities with rheumatoid arthritis on the top of the list of health priorities. When asked about oral health, one of the patients reports that it is:

> *"Not really one of them." (PATIENT 4 p2)*

5.9.3.9 Other

This topic was always kept free by the interviewer for any new topics that might emerge from the discussions. As the patients mentioned new topics, these new topics were noted in the "Other" column. When no more new topics emerged for three consecutive patients, the research team agreed that saturation was reached. The new topics that emerged from the interviews and were added to the initial topic guide were:

- Comorbidities/Health priorities

- Delayed treatment

- Financial compensation

Some of the topics and themes were merged between each other or reformulated as the discussions shaped the results of interviews. The full list of themes was presented in Figure 13 - Qualitative interview themes

Several patients reported that they would like to receive a report with the results at the end of the study.

5.10 End summary of qualitative results

The main findings of this interview process can be summarized by taking into consideration the specificities of this particular patient population. The sample that consented to take part in the interview process was fairly representative for the patient population with RA in terms of gender, age, time since diagnosis with rheumatoid arthritis, etc. The patients expressed their personal experiences regarding rheumatoid arthritis and the impact of this condition on their quality of life. Rheumatoid arthritis presented a direct effect on the patient's physical health (through pain, swelling, morning stiffness) and indirect effect through the side effects of the medications. Furthermore besides the impact that RA had on the patient's physical health, the patients reported on how the condition affected their emotional well being as well as the influence it had over their socio-economic

status as a consequence of reduction of work and/or early retirement based on disability.

Several patients related their experiences about developing coping strategies and trying to find new ways of doing the things that they used to do before being diagnosed.

Although many participants acknowledged the importance of good oral health and its potential impact on general health, when compared to rheumatoid arthritis and the other comorbidities that they have to manage to live with, oral health seemed to fall back on their list of healthcare priorities.

The patients identified a number of hindering factors that might impact their ability for study participation and some of these factors were addressed by changes of the research protocol.

6 Discussions

6.1 Feasibility

The OPERA study was developed with the main objective of assessing the feasibility of an interventional trial that would aim to assess the effectiveness of periodontal treatment in patients with rheumatoid arthritis. The outcomes presented in this study are related mainly to the feasibility findings, including but not limited to patients' compliance, recruitment, dropout rate, logistic challenges and the values and perceptions of patients with regards to study participation.

Any analysis of the clinical endpoints, must take this into consideration especially in terms of statistical power calculation of the population sample. Mainly descriptive statistics were presented. Results of statistical tests including the p-values should be interpreted with caution.

As with any interdisciplinary research, one of the main challenges was to successfully manage the effective communication, leadership and project management related issues with all the different stakeholders involved at all levels: rheumatology consultants, periodontology consultants, patients, patients representatives, dental hygienist, etc.

6.1.1 Methodology

The OPERA study has a number of advantages compared to other similar studies. The sample size of 60 patients and the six months follow-up period makes it the largest study on the effects of periodontal treatment on rheumatoid arthritis outcomes.

Table 45 – Associations between periodontitis and RA in interventional follow-up studies

Studies	Sample size		Follow-up	Results
	Treatment	Control		
Al-Katma, et al 2007 [9]	17	12	2 months	Decrease severity RA
Ortiz, et al 2009 [8]	10	10	2 months	Symptoms and signs improved
Okada et al 2013 [6]	26	29	2 months	Lower DAS28 and Pg serum levels
Ribeiro et al 2005 [5]	26	16	3 months	Decreased ESR
Pinho et al 2009 [120]	15	15	6 months	Unclear results

Table 45 presents a brief overview of several interventional studies that assessed the effect of periodontal treatment in rheumatoid arthritis disease markers [70, 121, 122] It can be observed that the results of these five studies were not always very clear, the sample sizes were small and the follow-up period was maximum six months [5, 6, 8, 9, 120]. This could lead towards highlighting the potential challenges of an interventional trial with this type of research design.

6.1.2 Recruitment procedures

In the beginning of the recruitment process standard recruitment letters were designed for patients' recruitment. This was requested by the clinical team from Queen Elizabeth Hospital Birmingham. A number of issues were identified regarding this approach. Some patients sent back empty response letters without marking any option; meanwhile other patients ticked both available options. Other letters were returned late to Birmingham Dental Hospital or were lost in the post. Another problem was represented by the fact that these standard letters were sent out to the patients that were booked for the following weeks clinics. Often these lists suffered alterations over one week time, having some patients rescheduling their clinical appointments to a later date and other patients moving them forward to the week in discussion.

After a trialing period of three months, based on the experiences, the research team decided that there is no added advantage in using the standard letters.

Another challenge was represented by the limited allocation of human resources in research as well as potentially conflicting trials that were recruiting patients in the same period.

This was evidenced at City Hospital Birmingham where only one research administrator allocated for patients recruitment for all the clinical trials that were running in parallel in the Rheumatology Department. This led to having one or two patients consented each week. Having a clear deadline set in place for the financing of this project, the time constraint was considered as one of the key aspects in running the trial as efficiently as it was possible. The solution to speed-

up recruitment was to involve the author of this thesis to personally recruit patients across all the recruitment sites. This approach led to a dramatic increase of study participation with over 10 recruited patients per week.

Ultimately, a member of the research team directly involved in the trial was required to be present and directly consent patients for efficient recruitment.

6.1.3 Sample characteristics at Screening

The patient population was represented mainly by women at postmenopausal age.

This finding was consistent with the scientific literature as two thirds of the patients with rheumatoid arthritis are women [122, 123]

In terms of ethnicity, the cohort was represented by an ethnically diverse population. This can be due to the fact that Birmingham area is home for a multiethnic and multicultural population. This can be considered one of the strengths of the study in terms of generalizability of the findings.

6.1.4 Sample characteristics at Follow-Up

The basic demographic characteristics of the randomized patient population are consistent with those of the screened population.

Both the Immediate Treatment and Delayed Treatment groups presented consistently higher values for blood pressure. This finding was to some extent surprising as all the screened and randomized patients were in long term care of a

rheumatology specialist. After discussing with the members of the research team, regarding this finding, the clinical consensus was that this was attributable to the "white coat syndrome" and the potential levels of anxiety represented by the dental visit. All the patients were being treated and monitored by specialist rheumatologists on a regular basis and consistently high values of blood pressure would have been noticed on the occasion of these visits. This information can be corroborated with the clinical data from the rheumatology clinics.

6.1.5 Logistics and follow-up appointments

The protocol for the OPERA study (Appendix 1: Study Protocol) established that the intervention for the Immediate Treatment Group is carried out at maximum three weeks after randomization. This however was not possible in most of the cases. The reasons for the delay were either technical or patient driven.

The technical reasons for the delay were represented by the challenges in assuring communication and logistics between the several stakeholders involved: OPERA was a trial that was led by the Oral Surgery Department from Birmingham Dental Hospital however the treatments for the patients were delivered by the Hygienist from the Periodontology Department. This raised a number of challenges in booking the patients list. A different procedure was set in place for booking patients for the Screening Visit, a different one for the Follow-up Visits and a different one

for the Treatment Visits. Timely and effective communication was key for success between all the factors involved.

Birmingham Dental Hospital was moved into a new building in March 2016. This did not have a major impact on the running of the OPERA Study. It affected some of the latest appointments but most of the patients finished the study before the move.

Another reason for delays was also represented by the delays requested by patients. As several patients had ongoing clinical appointments for several numbers of comorbidities, occasionally these appointments overlapped with the appointments from the Dental Hospital. In a large majority of occasions the appointments from the Dental Hospital were postponed, giving priority to the clinical appointments from the other hospitals. On other occasions, the patients were unable to attend their appointments because of flare-ups of their rheumatoid arthritis or just simply feeling generally unwell. Holidays or other types of commitments of personal nature also had an impact on delivering the study between the given time limits.

The patients were consented on Mondays at Queen Elizabeth Hospital Birmingham and Tuesdays at City Hospital Birmingham. Wednesdays to Fridays the screening and follow-up appointments were taking place at Birmingham Dental Hospital.

There was also a limitation of the logistic capacity of the number of patients that were possible to be seen on a day. The clinics at Birmingham Dental Hospital started every morning at 09:00 however one of the characteristics of rheumatoid arthritis is represented by morning stiffness. As a consequence the majority of patients requested for their appointment to be booked only after 10:00 am.

The appointments on the dental clinic lasted approximately one hour, being followed by the ultrasonic assessment, which lasted for approximately half an hour. In the dental clinic, the patients received all the clinical examinations and the biological samples were collected as described in the Methods Chapter.

The biological samples that were collected were processed in the Biology Laboratory of The University of Birmingham School of Dentistry. The processing of the samples took approximately one hour therefore the last patient had to be booked for no later than 15:00 hours to allow enough time for the clinical assessments and the processing of the biological samples.

Several patients presented significant delays in their appointments. The study protocol established that after consenting for treatment, the patients were randomized to one of the treatment arms and they received their first appointment with the Dental Hygienist two weeks after the screening visit. In practice this was not always feasible as often patients were not free in the exact given time frame. Furthermore other delays were caused by issues relating to staffing and waiting times at Birmingham Dental Hospital or patients cancelling appointments on short notice without being able to find a new appointment on a close enough time scale.

This was especially the case for the first appointment with the Dental Hygienist. In case a patient fails to attend the appointment with the Dental Hygienist, Birmingham Dental Hospital's policy is to discharge the patient and send a letter to the referring dentist. As the referring dentist for this study was also from the Dental Hospital, if a patient failed to attend the appointment with the Hygienist it often took a long time until the information was forwarded to the members of the research team and they managed to book a new appointment for the patient. This has led to significant delays for the first appointment with the Hygienist and as a consequence for the first follow-up appointment in the study. As the first follow-up appointment (Visit 2), according to the study protocol should have taken place at three months after the final treatment performed by the Dental Hygienist (for the Immediate Treatment Group) and three months after the one appointment with the Hygienist (for the Delayed Treatment Group) this often took place much later. As illustrated by Table 10 - Time spent between follow-up appointmentsit took a median of 1.5 months for the patients to see the Hygienist for the first time. The protocol required for this period to be no longer than 2 weeks. The treatment for the Immediate treatment group took approximately 2 weeks. These delays lead to an average waiting time of 5 months from Baseline to Visit 2. For the final visit (Visit 3) the delays were less severe with a median of value of 2.9 months for the Immediate treatment group and 3.2 months for the Delayed treatment group. On average a patient spent over 8 months as part of the study, instead of the minimum of 6 months.

6.1.6 Loss to follow-up

The number of patients that was lost to follow-up was greater in the Immediate Treatment arm, compared with the Delayed Treatment Group. The first follow-up visit which took place at 3 months from the end of treatment was attended by 26 patients in the Immediate Treatment group and 27 in the Delayed Treatment group For the last follow-up visit that took place 3 months from Visit 2 there were only 23 patients in the Immediate Treatment group compared to 26 in the Delayed group. To sum-up, by the end of the study there 7 patients were loss to follow-up in the Immediate Treatment group and 4 patients in the Delayed Treatment group.

It would be reasonable to hypothesize that once the patients received the periodontal treatment, their interest in study participation decreased or, based on the findings from the qualitative interviews the treatment experience discouraged the patients for further study participation. This would be in line with some of the patient's dental phobia on one hand and the discomfort created by the multiple attendances in the Dental Hospital which on the other hand, as reported by some of the participants in the qualitative interviews.

6.1.7 Medication changes

Several patients from both treatment groups had changes in their rheumatologic treatments during study participation. This could have potentially influenced the outcomes in terms of rheumatologic disease activity (DAS28 and ultrasounds) from Baseline to the Follow-up visits.

There was an ethical dilemma in requesting no change in medication for the study participants, especially considering the fact that this was a feasibility study that aimed to assess the feasibility for a larger trial, in a real world setting with multiple participating study sites. The frequency for medication changes is something that reflects the realities of this patient population and it would have been ethically and logistically unfeasible to restrict this for the purposes of a study with this design.

6.1.8 Missing data

Paragraph 5.5 reports on the missing data from the randomized patients. The missing data can be divided into clinical and non-clinical data.

In terms of clinical data there are two groups of clinical information relevant to this project: periodontal data and rheumatologic data.

In terms of periodontal endpoints, one patient had missing data at randomization. This was due to the fact that the patient presented gingival overgrowth and the research dentist performing the clinical examination could not finish the full mouth probing as per protocol. The patient was referred to the Periodontology Department from Birmingham Dental Hospital where the diagnosis for periodontitis was confirmed.

In terms of rheumatologic endpoints the two main clinical areas of interest were for DAS28 and ultrasounds.

For Baseline there were 2 patients (3.33%) – one for each treatment arm with missing DAS28 data. This came from the way DAS28 is being calculated. The

methodology for calculating DAS28 was presented in paragraph 4.7.3 Disease Activity Score (DAS28).

The Baseline DAS28 was calculated using the tender and swollen joint scores obtained at the Baseline visit together with the patient's visual analogue scale score (VAS) and the value of the ESR. The ESR value was obtained either from the results of the blood tests from the rheumatology clinic – when the patient was consented – either from the blood tests performed during the Baseline screening – if there was no ESR test at the rheumatology clinic.

Occasionally, with some of the patients, there were technical difficulties in collecting blood during visits in the dental clinic. In a number of occasions the blood tubes were mislabeled and the results were lost between the laboratory and the hospital. The research team aimed to place measures for quality control to prevent most of these situations but in a number of occasions this was not possible.

The other clinical rheumatologic endpoint with missing data was represented by the ultrasound scores. In a number of occasions the ultrasound was not possible to be performed due to technical issues represented either by the unavailability of the ultrasound machine or the lack of an appropriate room to perform the examination. Furthermore as the ultrasound assessment was done on a different clinic than the periodontal examination, occasionally the patients opted to leave before the ultrasound assessment started because of lack of available time.

Some of the patients complained regarding the large amount of questions from the questionnaires or the fact that occasionally the questions overlapped or felt repetitive. Furthermore, some patients expressed their preference to complete the

questionnaires at home and post them to the research team but occasionally they failed to do so. This could potentially explain the reasons for the missing data from the questionnaires.

6.1.9 Qualitative methodology

Some of the disadvantages of the one to one interviews are related to the potential recall bias and the patients answers can be influenced to some extent by their level of and health literacy. Level of income and the social economic gradient could also play a role in the responses provided by the subjects of the study.

In order to insure methodological consistency for the interviews, an independent researcher with expertise in qualitative research methods observed and provided feedback for some of the interviews that were conducted.

To control for the potential bias from the author of this thesis in terms of data analysis and interpretation, an independent researcher reviewed the transcripts and the framework analysis and the results were compared and agreed by consensus.

The framework analysis for this study was conducted manually. For further research it might be worth exploring the option of using software such as NVIVO and compare the results with the manual work [124].

6.1.10 Qualitative results

The qualitative sample for this study was diverse and heterogeneous in terms of demographics and clinical characteristics. Furthermore it was also comprehensive in terms of representing patients who did not consent to take part in the clinical trial as well as patients who consented to take part in the trial; as well as patients from the immediate treatment and the delayed treatment groups.

Their views were varied and could be influenced by their age, time spent since diagnosis with rheumatoid arthritis, socio-economic status, level of education and health literacy.

Despite these differences, most of the patients seemed to agree on the idea that rheumatoid arthritis is a condition that had a major impact on their quality of life. The stories are extremely rich with personal views and emotions reflecting the very personal and unique ways in which RA had an effect on their quality of life, level of income, emotional and psychological health. One of their main concerns seems to be represented by the ability to have a "normal life" as much as possible - to live independently, autonomously and pain free.

In many cases, they have to balance their life around the treatment they receive for RA as well the treatments for a set of comorbidities: this involving several medications, hospital visits, etc.

Considering all these factors, it can be easier to understand that most of these patients did not report on having oral health as a priority. This finding, however, can be adjusted for different age groups as well as for length of time that a certain patient has spent since the RA diagnosis.

In the light of these results, a future clinical trial should take into accounts the priorities and preferences that are driving this particular patient population. An interventional trial with a design involving multiple clinical follow-up appointments should target the specific segments of the patient group that would most welcome this design. This would increase the chances for a higher patient compliance and lower dropout rate.

6.1.11 Technical aspects

One of the most interesting lessons learned through this trial was related to the complexity of handling all the logistical and technical aspects of a study that involves several NHS Trusts and specialists from different clinical backgrounds. From rheumatology consultants to dentists and research nurses, everybody's commitment and willingness of cooperation was necessary to implement the study in an efficient way.

One of the nurses involved in the study, mentioned the fact that the hospital is an NHS Hospital and that patient's treatment takes priority before research. This has led to a discussion that highlighted the importance of understanding the values, motivations and priorities that are driving each member of the research team. It is crucial to understand these in order to be able to deliver a high quality service. Regular follow-up meetings with the research team were held in order to assure that everybody is well informed about the progression of the study and in case there are any problems identified by any member of the research team, the solutions can be identified and implemented together. Clinical research is by its

very nature teamwork. One of the ideas that emerged from those meetings was related to the fact that the NHS Constitution states that the "NHS aspires to the highest standards of excellence and professionalism… through its commitment to innovation and to the promotion, conduct and use of research to improve the current and future health and care of the population" [125].

In line with this idea, it would be worth mentioning the concept that clinical research could also be analyzed as part of health services research. Using Donabedian's concept in health services research relating to Structure, Process and Outcome it would be worth further developing a framework to assess clinical research capacity from the same perspective [126, 127]. That analysis would be beyond the aims of this thesis but it is an anecdotal finding that is in line with the previous research conducted by the author of this thesis.

6.2   Clinical outcomes

The type of clinical endpoints that are assessed has important implications for the design of the protocol of any interventional trial. The endpoints determine also the sample size and any statistical analysis has to be sufficiently powered in order to be able to assess these endpoints.

One of the most important clinical endpoints to evaluate the effects of rheumatoid arthritis on the long term is represented by radiological assessments of the bones. This however, implies that the patients have to be followed-up for a long period of time to be able to detect changes in the shape and structure of the bones. Setting

up a clinical study that would have a control group that would not receive treatment for periodontal disease for a long period of time would likely be considered unethical.

Time spent since diagnosis with rheumatoid arthritis could also play a role in determining the potential benefit of periodontal treatment. The patients that were interviewed as part of the qualitative part of the project, spent on average 21 years since the moment they were diagnosed with rheumatoid arthritis until the moment they were interviewed in the OPERA Project. The range of years spent since RA diagnosis starts from 1 year to 60 years in the qualitative patient sample. Evaluating the effects of an intervention over six months for a patient that suffered of a condition for over 20 years can be difficult.

6.2.1 Surrogate endpoints vs hard endpoints

It is common practice in clinical research to use surrogate endpoints as a measure for chronic conditions as in most of the situations it would be unethical or unfeasible to use "hard endpoints" to evaluate the effect of exposure over the outcome. This problem was raised also in 2012 in an official statement of the American Heart Association (AHA) regarding the associations between periodontal disease and atherosclerotic vascular disease (ACVC) [128]. The statement called for further, high-quality research and highlighted the weaknesses of several studies focusing on surrogate endpoints and the lack of evidence for the sustainability of the response to treatment over time.

There can be several reasons for having a large number of studies focusing on surrogate, short-term endpoints instead of those that are clinically more relevant. These reasons can be ethical, financial or even related to feasibility for a long-term follow-up.

6.2.2 Rheumatologic endpoints

6.2.2.1 DAS 28

Although widely used across research studies and clinical assessments, the rheumatoid disease activity score (DAS28) has certain limitations [129]. It is a score that can fluctuate from one day to another. Also, the visual analogue scale (VAS) can play an important role in the results of the final score. The calculation methods of the DAS28 score were presented in the Methods Chapter. The VAS is prone to some bias in terms of how every person perceives pain in a different way. Pain can be perceived differently depending on the patient's age, gender, culture, ethnicity, or time spent since diagnosis with rheumatoid arthritis. Patients that spent a long time with the condition, could present a lower sensitivity to pain as their get more accommodated with the sensations of pain than patients that are newly diagnosed.

6.2.2.2 Ultrasound

Ultrasonic assessments were considered a non-invasive and convenient method of monitoring the levels of inflammation from the joints. Over 13.000 images were recorded in Gray Scale and Power Doppler for the randomized patients in the two

groups. Initially were taken longitudinal images of the wrists knuckles and toes,- all of these bilaterally. The ultrasonic assessment of the toes proved to provide certain difficulties. The patients had to remove their shoes, socks and/or tights and get on a bed. This was not very comfortable for most of the patients, especially in wintertime when they had difficulties in removing the winter shoes/boots and several layers of clothing. Most of the patients did not present any significant ultrasonic activity in their toes, which is why it was decided, together with the rheumatology specialists to record and assess the ultrasound images of the wrists and knuckles only – without the toes.

The large number of ultrasounds made it logistically difficult to perform a separate grading for each and every patient for each visit to assess the inter-observer validity and reliability. It was decided instead to create separate assessments for different grading of joints and compare the findings between the author of this thesis and a consultant rheumatologist with expertise in ultrasonic assessments. To improve validity and reliability, training sessions were held periodically between the author of this thesis and the consultant rheumatologist as described in section 4.12 Ultrasound

A number of randomized patients received intra-articular steroid injections as part of their rheumatologic treatment during study participation. This was a factor that could potentially have a high influence on the level of synovial inflammation visible on the ultrasound images.

6.2.3 Periodontal endpoints

There is a lack of consensus in the scientific literature regarding the definition of periodontal diagnosis and universal criteria for successful periodontal treatment [23, 28, 29]. In terms of clinical practice, patients who receive periodontal treatment are required to be compliant and have a good oral hygiene to maintain periodontal health [130-132]. This leads towards skewed results and potential selection bias in the general population in terms of success rates for periodontal treatment. The patients in this project were offered periodontal treatment and education about the importance of good oral hygiene as well as specific methods of maintenance that are designed specifically for patients that have mobility problems or problems regarding the grip of small objects – caused by the joint damage in rheumatoid arthritis.

6.2.3.1 Plaque

One of the limitations of this study was represented by the lack of recording of the plaque levels. As this was a feasibility study and the clinical endpoints are not considered to be primary outcomes, the decision to not record plaque was taken in the beginning of the study as to not increase even longer the duration of the clinical appointment in the dental chair and to avoid the need and inconvenience of using revelator. Without recording the plaque index, the appointment was already approximately one hour long and sitting for too long in the same position was a cause of complain for several patients as this caused them discomfort because of

their condition. From a clinical perspective, any further trial should consider recording longitudinal data on plaque levels.

The hygienist that performed the periodontal treatment reported that several patients presented a poor level of oral hygiene and difficulties in maintenance as illustrated at their follow-up appointments.

This is reflected by the clinical data presented in paragraph 5.6.2 Periodontal parameters at follow-up. Clinical endpoints like: Proportion of sites/mouth with PPD ≥ 3mm, Proportion of sites/mouth with PPD ≥ 5 mm, Proportion of teeth/mouth PPD ≥ 3mm, Proportion of teeth/mouth PPD ≥ 5mm and PISA (Periodontal Inflamed Surface Area) all presented a statistically significant decrease in the Immediate treatment group from Baseline to Visit 1 but in lack of maintenance this decrease was not sustained for Visit 3.

The effectiveness of periodontal treatment in patients with chronic conditions is becoming a source of more and more intense debate in the scientific community.

While randomized controlled trials are considered the "gold standard", the methodological dilemmas faced by the field are getting increasingly complicated in todays' research environment. Engebretson et al presented the results of a randomized controlled trial of 514 patients with diabetes and periodontal disease [133]. The study design was similar to the OPERA study with half of the patients receiving intense non-surgical periodontal treatment while half receiving only oral hygiene instructions. The patients were followed-up at three months and six months from baseline. After the six months follow-up the authors concluded that "nonsurgical periodontal therapy did not improve glycemic control in patients with

type 2 diabetes and moderate to advanced chronic periodontitis" and that the results "do not support the use of nonsurgical periodontal treatment in patients with diabetes for the purpose of lowering levels of HbA1c."

This study has led to a response authored by 21 of the most respected and acknowledged authorities in the field of periodontology [134] where they provided a series of concerns regarding the findings of the study published by Engebretson et al.

The first concern raised by the group of the authors was related to the fact that patients at Baseline had already a good level of glycemic control, therefore it would be difficult to expect a significant treatment effect after the periodontal treatment was delivered. Similar problems were faced by the OPERA study (in terms of inclusion/exclusion criteria). Although the patients needed to have some extent of disease activity in order to be randomized for treatment, they also have been on an ongoing effective background treatment. In general, all the trials encounter a similar challenge whereas the treatment is executed against a background of effective medical treatment available.

The second concern was that the conclusions of the study are not valid because the periodontal treatment failed to reach the accepted standard of care, more precisely the mean probing reduction was not significant.

This conclusion could potentially be applied also in case of OPERA as presented in Table 17 and Table 18. The mean (SD) probing depth for the Immediate treatment group at Baseline was 3.4 (0.7) mm followed by 3.1 (0.9) mm at Visit 2 and 3 (0.8) mm at Visit 3.

This however, does not reflect the results of the cumulative probing depth in the OPERA study where the values were 64 [44, 80] mm at Baseline and decreased to 42 [22, 68] mm at Visit 2 and 33 [21, 73] mm at Visit 3 (p =0.002 for both visits).

When treatment is being delivered to a population that is not selected for compliance with oral health measures, the treatment results may be less than ideal.

The third concern of the review group was that "pronounced obesity would mask any decrease of inflammatory response caused by successful periodontal treatment." The mean BMI of the patients in the study delivered by Engebretson et al, was 34.7. The reviewers suggest that there is evidence to support the hypothesis that systemic inflammation persists in obese patients after non-surgical periodontal treatment [135].

The mean (SD) BMI of the patients from the Immediate treatment group in the OPERA study was 31.0 (7.9) (Table 13).

6.2.3.2 Optimal periodontal treatment

A large number of professional societies around the world, created specific guidelines to describe the optimal care pathway for periodontal treatment.

The British Society of Periodontology (BSP), the American Academy of Periodontology and The Scottish Dental Clinical Effectiveness Program (SDCEP) are the main professional organizations to provide these guidance in the English-speaking world.

The guidelines of the British Society of Periodontology (BSP) and the American Society of Periodontology (ASP).

According to these guidelines the treatment plan for periodontal treatment is structured as follows:

- Assessment and Diagnosis

- Patient behavior change

- Non-surgical therapy

- Management of Local Plaque-retentive Factors

- Periodontal surgery

- Long Term Maintenance and support

The professional organizations for periodontology in the UK and the US agree that optimal levels of treatment can only be achieved in patients that are fully compliant with oral hygiene instructions [136-138]. Furthermore it has been also highlighted that prior to periodontal surgery, patient's access for cleaning has to be maximized by removing any potential restorative/orthodontic work that could hinder optimal access for cleaning.

As these factors constitute increasing practical difficulties in a patient population with chronic systemic conditions such as RA, it raises the questions regarding the feasibility of larger interventional studies that could assess treatment effectiveness.

6.3 Patient reported outcomes

When examining patient reported outcomes, reporting bias is one of the possible factors that need to be taken into account. The patients completed a 17 pages questionnaire at each visit (Baseline, 3 Months Follow-up and 6 Months Follow-up). Most of the patients reported that it was a burden because of the large number of questions, some of which were repetitive. Also, as most of the patients were elderly, they reported difficulties in reading the print without glasses or holding the pen for too long – because of joint damage.

Also, as illustrated by the qualitative interviews and the findings from the literature the patient relevant endpoints can be sometimes different than the clinician driven endpoints [92, 97, 98]. In terms of rheumatoid arthritis – one of the most important endpoints for the patients was lack of pain and freedom for mobility and autonomy. Whilst disease activity score and markers of inflammation represent the clinical endpoints from the specialist's perspective, the patient reported outcomes play at least an equally important role that needs to be taken into account when designing a trial. In the same way, whilst periodontists argue about establishing a gold standard for diagnosis of periodontal disease as well as criteria for success of treatment, the patient group from the OPERA study did not consider oral health an absolute health priority considering all the comorbidities that they have to struggle with.

> *"If I had to have teeth out, I have to have them out and that's the end of it."*
>
> (PATIENT 4 p7)

On the other hand, those patients that do consider oral health as a priority reported that once diagnosed with periodontitis they would prefer to get treatment as soon as possible and the maximum delay that is acceptable for them would not be longer than six months.

6.4 Contamination

As described through the section 5.9 some of the patients that were diagnosed with periodontal disease and were assigned to the control group, reported that did not wish to wait until they would have received delayed periodontal treatment as part of the study but seek help elsewhere in case the delay would have been for too long.

This could potentially contaminate the results of a future interventional study. One of the challenges of this pilot study, and any further interventional study with a similar design are represented by the fact that once the patients are revealed their periodontal diagnosis, they could potentially seek help outside the study in case they are allocated to the control group. The likelihood of this could increase by the increase of the length of the waiting time for treatment for the delayed patient group.

This topic leads the reader to the feasibility and ethical dilemma of running a larger, multicenter randomized controlled trial that aims to assess the effectiveness of periodontal treatment in reducing RA disease parameters.

6.5 Feasibility/Ethical dilemma

The results of this pilot study are crucial for the development of the protocol and methodologies for a larger clinical study. As most of the patients were diagnosed with rheumatoid arthritis several years ago, a change in their disease activity level over a six months period of the study is difficult to evaluate. A longer observation period would be desirable from a methodological perspective; however setting up a control group that receives a delay of the periodontal treatment for longer than six months would not be ethical. Once diagnosed, most of the patients desired to be treated as soon as possible. Although some patients expressed their confidence in the research team and the advantages of the close, periodical monitoring, the longest period of waiting from the patients perspective would be around six months to one year.

6.5.1 Delay of treatment

The higher numbers of drop outs in the Immediate treatment group presents one of the methodological challenges of such a study - to keep all the patients, from both treatment groups engaged and motivated for study participation for the duration of the entire study.

As illustrated by personal correspondence with members of the Rheumatology Unit from the Karolinska University Hospital from Stockholm, the delay of treatment is an important ethical conundrum – a topic that requires further investigation. The delay of periodontal treatment for a patient that is diagnosed with the condition is

considered unethical in Sweden. This is the reason why a similar project to OPERA would have not received ethical approval in Sweden, as reported in the correspondence (Serban, ST. 08 august 2016, correspondence with Karin Lundberg, PhD Senior Scientist Rheumatology Unit, Karolinska Institute, Stockholm).

The patients' waiting list for periodontal treatment in Birmingham Dental Hospital could be longer than six months, which is why delaying the treatment in the control group, was considered ethical in this setting.

Cluster randomization of different hospitals (or NHS Trusts in the case of the UK) would represent a possible research design for a larger study that would avoid this problem. If the prevalence of periodontitis is considered normally distributed across the clusters and the patients were not diagnosed for periodontitis at baseline in the control clusters but only in the intervention clusters. The clusters would be compared in terms of RA disease activity over time. This approach could avoid the ethical conundrum of delay of treatment. However this design would create other challenges such as the number of possible confounding factors that could influence the outcomes.

7 Conclusions and recommendations

7.1 Conclusions

When designing the protocol for an interventional clinical trial that involved a vulnerable population, there can be many unforeseen challenges. The findings from the qualitative part of this study are highlighting several potential challenges as well as solution that should be taken into account when designing a larger, interventional study to assess the effectiveness of periodontal treatment in patients with rheumatoid arthritis.

While analyzing these results, they should be regarded in a corroborative manner with the feasibility findings from the CONSORT flowchart and the quantitative results from the clinical data. Considering the relatively advanced age group of this population, their healthcare priorities are in line with the status of their general health. The patients highlighted the importance of independence, mobility, lack of pain as factors that shape their decision-making processes in terms of the healthcare services that they choose to access.

As presented in section 6.2.3.2 Optimal periodontal treatment, professional organizations in periodontology like the British Society of Periodontology (BSP) and American Academy of Periodontology (AAP) highlighted the importance of behavior change and maintenance to achieve optimal levels of success for

periodontal treatment. For future directions of research it would be desirable to investigate how feasible would be behavior modification for a patient population that already is suffering with a chronic debilitating condition and potentially with a large number of comorbidities, besides periodontitis.

7.1.1 Mobility

Mobility is one of the main barriers for access for patients from this population group. As the gender balance is more inclined towards females who are more advanced in age, their ability to get to dental care service providers might be impaired. As some of them had to take early retirement because of their condition, their income level was also affected which subsequently influenced their choices and priorities regarding the healthcare services that they would access.

7.1.2 Health priorities

As several patients reported a number of comorbidities besides rheumatoid arthritis, this is also one of the factors that influenced study participation. When asked to list in order of importance their health priorities, most of the patients listed cardiovascular disease, respiratory conditions or problems regarding mobility and pain. In most of the cases, oral health was not considered an important health priority compared to the other conditions that the patients are suffering with. Moreover because of the mobility problems, the patients reported difficulties to

include an additional dental appointment to their on-going several hospital appointments for their existing comorbidities.

7.2 Recommendations

- The planning of a larger, interventional trial should take into account the findings from this pilot, feasibility study.

- The qualitative and quantitative findings are reflecting some very specific problems of the patient group of interest such as access to care, comorbidities and health priorities. These factors might play an important role in the recruitment process as well as patients adherence to the study protocol.

- Some of the endpoints need to be evaluated both from patient's perspective and from the feasibility of monitoring perspective during the trial. Rheumatoid Disease Activity Score (DAS28) is prone to fluctuations in a short period of time and can be influenced by subjective measures. "Hard endpoints" that could be more objective are difficult to monitor over short period of time.

- The outcomes that the patients mentioned as most relevant for them were related to their ability to perform unhindered their day-to-day activities, which contribute to a good quality of life and that are driven by values such as autonomy and self-confidence. Patients often mentioned the "pain-free" life as a very important outcome. The patients seemed to express strong views regarding their desire to live their lives as independently as possible, like they were before they have been diagnosed with rheumatoid arthritis.

- Delaying treatment for longer than six months for the control group would not be ethical nor acceptable from the patients perspective. A possible solution for this would be cluster randomization of Rheumatology Clinics or Hospitals in case of a larger, multicenter study. Other issues however could arise in this situation regarding data collection and analysis.

- Patients who did not have a long time since their RA diagnosis could potentially present better compliance with the study protocol and present easier to monitor clinical endpoints.

- One of the key logistic solutions is to create a specially allocated research and treatment clinic. Patients should be screened, randomized, treated and monitored on the same clinic by clinical study personnel that are allocated full-time for the project. Potentially this clinic would include also the rheumatology consultation and treatment clinic in order to reduce any potential discomfort for the patients whilst maximizing efficiency of the resources from the research team.

8 Appendix 1: Study Protocol

Study number: RG_10-138

                                              REC 11/WM/0235

Study title: Outcomes of Periodontal Therapy in Rheumatoid Arthritis

Study pseudo name: OPERA

Version: 1.1

Protocol Date: 20/12/2013

Proposed Study start date: 6/1/2014

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1)   Introduction:

Rheumatoid arthritis (RA) is common chronic inflammatory disease that is characterised by inflammation in the joints ultimately leading to joint destruction and consequently functional impairment and disability. In addition, patients with RA are more likely to develop cardiovascular diseases such as heart disease and stroke and are therefore at an increased risk of premature death. Several studies now indicate that chronic periodontitis, a common inflammatory disease of the gums surrounding the teeth caused by bacteria in the mouth, can initiate and worsen inflammation in RA. A small number of small clinical studies in patients with RA have indicated that periodontal therapy aimed at eliminating gum infection can reduce joint and systemic inflammation in patients with RA. We therefore propose this clinical pilot study to study the effects of intensive periodontal therapy administered by a dental hygienist in a secondary care setting to patients with RA who also suffer from moderate to severe periodontitis. We will measure the effect of this intervention on several clinical and blood measures of RA and RA activity as well as on overall and oral health related quality of life. We will also assess how easy or difficult it is to recruit patients into such a study and how easy and acceptable patients find participation and compliance with the periodontal therapy

and the study procedures. We plan to evaluate this intervention in a larger definitive study, provided that the proposed pilot study is successful and shows promising results. If successful, treatment of gum disease in patients with RA could be an inexpensive and safe, non-pharmacological treatment with direct benefit for patients with RA in terms of RA severity and progression.

2) Scientific Summary

2.1 Background
RA is a chronic immune-mediated inflammatory disease associated with significant morbidity and, primarily due to cardiovascular disease, increased mortality. More than 500,000 people in England suffer from rheumatoid arthritis, with approximately 26,000 new cases being diagnosed every year. Chronic periodontitis is arguably the most prevalent chronic inflammatory disease of humans and several lines of evidence indicate that periodontitis may be a causal risk factor for RA. Effective and safe treatments for chronic periodontitis exist and a small number of preliminary studies have indicated that successful treatment of periodontitis may benefit patients with RA in terms of RA disease activity.

2.2 Plan of Investigation
We plan to conduct a randomized parallel-group randomized controlled clinical pilot trial of the short term effects of non-surgical periodontal therapy on RA disease parameters. Patients with established rheumatoid arthritis and moderate to severe chronic periodontitis will be eligible for inclusion. The intervention group will receive intensive non-surgical periodontal therapy with rigorous periodontal maintenance; the control group will receive oral hygiene instructions for the duration of the trial, and full therapy at the end of the study. Patients will be followed for 6 months. Outcome measures include clinical and serological markers of RA and disease activity, and general and oral health related quality of life.

3) Study aims
Our mid-term goal is to evaluate the effectiveness, cost-effectiveness and safety of intensive periodontal therapy and maintenance administered by dental hygienists in an intermediate/secondary care setting to reduce disease activity and improve function in RA. Our main hypothesis is that control of periodontal infection and inflammation by means of intensive non-surgical therapy administered by a dental hygienist will result in improved disease activity, function and QOL.

In order to be able to evaluate this hypothesis in a definitive trial, the present pilot trial will randomise RA patients who also suffer from moderate to advanced chronic periodontitis to intensive non-surgical periodontal therapy or delayed therapy. The objectives of this pilot trial are to assess the feasibility of the proposed protocol, to establish recruitment and retention rates, to gauge the acceptability of the intervention and study procedures to patients and to gather pilot data on the effect size and variability of the effect of the intervention. We plan to accomplish these objectives by pursuing the following specific aims:

3.1 Establish recruitment and retention rates

We will establish the proportion of RA patients in the target population that
(a) Meet inclusion criteria in terms of RA disease activity.
(b) Meet periodontal inclusion criteria.
(c) Are willing to undergo periodontal treatment.

This is important not only to assess the feasibility of the protocol and screening requirements for a larger definitive study, but also to gauge the potential impact of the intervention in terms of the size of the potential target population (note that this will only be determined by what proportion of RA patients meet periodontal criteria, the RA inclusion criteria only apply to the specifics of a clinical trial).

3.2 Gauge the relevance and acceptability of the intervention and study to patients

We will conduct semi-structured qualitative interviews with participants recruited into the study, as well as with participants who refused to participate even though they were eligible. The results of these interviews will directly inform the design of a future definitive study by identifying barriers for recruitment, issues related to acceptability of the study procedures as well as factors important to be included in quantitative assessments in a definitive trial.

3.3 Refine study protocol and logistics

Our experiences from this pilot study as well as feedback from patients will inform the design and planning for a potential definitive trial. This includes not only the study design itself in terms of eligibility criteria and study procedures, but also logistic aspects such as recruitment procedures and the coordination and timing of visits between rheumatology and periodontal clinics.

3.4 Gather pilot data on effect size and variability of outcome measures

Data on the effectiveness of non-surgical periodontal therapy on RA disease activity will be collected 3 months after treatment. Patients who do not respond after 3 months of treatment will be offered 'rescue' treatment as per standard of care (adjustment of DMARD therapy or treatment with biologics). All patients will be followed for 6 months to assess 'maintenance of benefit'. Collection of these data is crucial to evaluate if the intervention shows any promise to affect the outcomes of interest in the proposed NHS setting and if so, for sample size estimation for a definitive trial.

4)   Study background

4.1 Link between chronic periodontitis and RA

We have recently reviewed the literature linking RA and chronic periodontitis [2], showing a large number of studies that have indicated a positive association between the occurrence of periodontitis/tooth loss and RA, i.e., RA patients are more likely to have chronic periodontitis and have lost more teeth compared to

individuals without RA. In our own population-based study [1], having RA was associated with a four-fold increase in the odds of having periodontitis, after adjusting for potential confounders. Another recent longitudinal study from the US has, for the first time, shown an increased incidence of RA in individuals with periodontitis [7]. Interestingly, the recent recognition of the importance of anti-citrullinated protein antibodies in RA and the discovery that the major periodontal pathogen Porphyromonas gingivalis expresses peptidyl arginine deiminase (PAD), provides a plausible potential pathobiologic mechanism by which periodontitis may cause or sustain the inflammatory response in RA. PAD is an enzyme responsible for post-translational citrullination of peptide antigens on arginine residues [8], and microbial PAD deiminates arginine in fibrin found in periodontal tissue [9]. Individuals with periodontitis are exposed, therefore, to citrullinated antigens that might become systemic immunogens.[8] Interestingly, patients with periodontitis might have anti-citrullinated protein antibodies (ACPA) in the absence of any signs of RA.[7, 10] The levels of antibodies against P. gingivalis have been correlated with levels of ACPA in patients with RA.[11] Antibodies to citrullinated α-enolase are specific for RA [12, 13]; an immunodominant epitope in this protein that shows sequence similarity and cross-reactivity with P. gingivalis enolase could indicate a role for P. gingivalis infection in priming the autoimmune response in RA.[13]

Autoantigens modified by citrullination through exposure to periodontal pathogens [8] might sustain synovial inflammation in the context of untreated periodontitis. Given the high prevalence of chronic periodontitis in the UK population, chronic periodontitis may thus represent an important modifiable factor leading to increased RA incidence and severity. To date, three small intervention studies have indicated that periodontal treatment in patients with RA may have a beneficial effect on RA disease parameters, including the erythrocyte sedimentation rate [3-5] and an improvement in the Disease Activity Score (DAS28) [3, 4]. However, whether such benefits can be achieved by providing periodontal care in an NHS setting is unclear.

4.2 Current periodontal care
Currently periodontal care is provided within the General Dental Services (GDS) under the new dental contract (2006) and comprises oral hygiene instruction, scaling and root surface debridement and supportive care. It is categorised as a "band 2" procedure and amounts to 3 units of dental activity, with patients contributing approximately £42.00 to the cost of care. The Clinical Audit Committee of the Royal College of Surgeons of England classified periodontal diseases into 3 codes of complexity [14]. Under these guidelines, general dental practitioners are advised to only refer patients with relatively rare aggressive forms of periodontitis to specialist care. However, chronic periodontitis is underdiagnosed and under-treated in the GDS, for a variety of reasons including the limited availability of dental hygienists in NHS general dental practices [15]. Furthermore, specialist care is more intensive than that performed within the GDS [15] and the greater time spent and expertise employed within specialist environments results in greater periodontal stability [16]. Hence, we strongly believe that an

intermediate/secondary care setting employing dental hygienists is most appropriate for periodontal treatment of patients with RA in order to achieve successful outcomes. If periodontal care results in improved RA outcomes, then there would be significant patient benefit to be gained by including periodontal therapy within the RA-patient care pathway, and such treatment would have to be commissioned rather than referred to the GDS.

5)   Research Plan & Methodology

5.1   Overview:
To address the objectives and specific aims of this study, we propose to conduct a 6-month two-arm parallel group randomised controlled clinical trial. 60 RA patients with moderate to advanced chronic periodontitis will be randomly allocated to receive either non-surgical periodontal therapy with intensive maintenance therapy delivered by a dental hygienist (intensive therapy), or no therapy. Periodontal parameters and RA disease activity parameters will be assessed at baseline, three and six months. At the end of the 6-months study, patients in the control arm will be offered non-surgical periodontal therapy as per intervention group. Outcome evaluations will include measures of RA disease activity and disability, periodontal measures, as well as overall and oral-health related quality of life.

5.2   Study population and recruitment procedures:
Patients with established rheumatoid arthritis (RA) attending the outpatient Rheumatology services at City Hospital and Queen Elizabeth Hospital (scheduled to be moved from Selly Oak Hospital) will be contacted. General medical and rheumatologic eligibility criteria will be assessed and dentate patients meeting eligibility criteria will attend an outpatient periodontology clinic at Birmingham Dental Hospital. Dental eligibility criteria will be assessed and patients who qualify will be enrolled and randomised to the intervention or control group.

There are several challenges to evaluating the efficacy of a novel intervention to reduce disease activity of RA [17]. With the availability of effective treatments in RA, 'pure' placebo trials have become unethical. Hence, testing a new intervention against background therapy and early rescue have become standard practice. However, to be able to demonstrate efficacy of the new intervention, patients on background therapy have to have sufficiently active disease. We therefore propose an 'addon' design, whereby patients who have been on a stable DMARD regimen for at least 2 months and who have active disease (DAS28 score>=3.2) will be offered participation in the trial. If the disease is still active after 3 months of experimental treatment, patients will be offered 'rescue'-treatment as appropriate. We will also offer trial participation to patients with higher disease activity that would qualify for biologics according to NICE guidelines but who decline biologic therapy. Patients who are currently on a stable biologics regimen are eligible, because even though treatment with biologics itself may have beneficial effects on periodontitis [18], RA disease activity may be reduced by additional periodontal treatment [4].

5.3 Inclusion Criteria

•   Able and willing to give written informed consent and comply with the requirements of the study protocol.

•   Age 18+ years

•   Patients with rheumatoid arthritis (RA) diagnosed according to the revised 1987 ACR criteria for the classification of RA

•   DAS28 score ⩾3.2

•   DAS28 score >5.1 only if patient on biologics or patient unwilling to take biologics

•   Treatment with DMARD for ⩾ 3 months and stable dose for ⩾ 2 months

•   Generalized moderate to severe chronic periodontitis as evidenced by pocketing with clinical attachment loss (CAL>=4 mm on at least 2 non-adjacent teeth AND cumulative probing depth>=40mm). The threshold based on CAL is consistent with a recently proposed case definition [19]. Cumulative pocket depth is the sum of the deepest probing depths of at least 4mm on each tooth [20].The proposed threshold ensures a minimum number of teeth with deep periodontal pockets, e.g., a patient who has 8 teeth with 5mm pockets would meet this criterion.

5.4 Exclusion Criteria

•   Rheumatic autoimmune disease other than RA, or significant systemic involvement secondary to RA (including but not limited to vasculitis, pulmonary fibrosis or Felty's syndrome). Secondary Sjögren's syndrome or secondary limited cutaneous vasculitis with RA is permitted.

•   History of, or current, inflammatory joint disease other than RA (including, but not limited to, gout, reactive arthritis, psoriatic arthritis, seronegative spondyloarthropathy) or other systemic autoimmune disorder (including, but not limited to, systemic lupus erythematosus, inflammatory bowel disease, scleroderma, inflammatory myopathy, mixed connective tissue disease or any overlap syndrome).

•   Diagnosis of juvenile idiopathic arthritis (JIA) or juvenile rheumatoid arthritis (JRA) and/or RA before age 16.

•   Any surgical procedure, including bone/joint surgery/synovectomy (including joint fusion or replacement) within 12 weeks prior to baseline or planned during study

•   Significant concomitant disease, which would preclude patient participation in the investigators' opinion.

•   Intra-articular or parenteral glucocorticoids within 4 weeks prior to baseline

•   Any dental condition that would preclude, in the investigator's opinion, participation in the trial (including but not limited to restorations impairing oral hygiene or instrumentation, need for extractions or extensive restorative work)

•   Periodontal treatment (surgical or non-surgical, excluding supragingival cleanings) within 12 months prior to baseline

5.5   Recruitment

The outpatient Rheumatology departments at City Hospital and Selly Oak Hospital together care for approximately 5000 RA patients annually, with a mean age of approximately 50 years. We estimate that at least 20% will satisfy rheumatologic eligibility criteria. 94% of UK adults aged 45-54 years are dentate, of which 52% have CAL >3.5 mm and 61% have at least one pocket (PD > 3.5 mm) [21].

These figures demonstrate that the prevalence of chronic periodontitis in the UK is high, and it is expected to be even higher among patients with RA. However, it is difficult to predict what proportion of RA patients will meet dental eligibility criteria, and establishing this proportion is therefore one specific aim of this pilot study. Based on these data we would estimate that 10% of eligible RA patients will fulfil periodontal eligibility criteria. Thus, we expect to be able to recruit 60 patients into the study within 12 months.

5.6   Intervention

Patients randomised to the intervention group will receive a course of non-surgical periodontal therapy, completed in 2-3 sessions within 3 weeks of the baseline rheumatologic assessment. Non-surgical periodontal therapy will be delivered by a dental hygienist at Birmingham Dental Hospital. Following oral hygiene instruction, scaling and root surface debridement (RSD) will be performed under local anaesthesia using ultrasonic scalers and hand instruments as appropriate. At three and six months following scaling and RSD, supragingival scaling and prophylaxis will be performed and all sites with 4+mm probing depth and bleeding on probing or sites with 5+ mm probing depth will be reinstrumented.

The control group will receive oral hygiene instructions only during the study period. In the event of an increase in probing depth or clinical attachment loss of more than 2 mm (active site) between baseline and 3 month visits, site-specific rescue treatment will be performed. All patients in the control group will be offered the same periodontal therapy as the intervention group after study completion (6 months after baseline).

5.7   Treatment allocation

Treatment allocation will be based on stratified randomization by ACPA status (positive or negative).. The randomization list will be generated by the Birmingham Clinical Trials Unit (BCTU). Following confirmation of eligibility for the intervention and informed consent, patients will be randomised when they attend the first treatment appointment with the hygienist. The hygienist will phone the randomisation service run by BCTU and the patient will be randomised in either the control or the intervention arm.

5.8   RA management during trial

In line with current recommendations for clinical trials in RA [17], patients will be required to have been on DMARD medication for at least 3 months (stable DMARD dose for at least 2 months) before study enrolment to be eligible. Periodontal

treatment will then be added to the existing background treatment in patients randomised to the intervention arm. Medical treatment (DMARDs and/or biologics) should not be modified until the 3 months follow-up. If the DAS28 remains >=3.2 at the three months follow-up, modification of DMARD regimen or treatment with biologics will be discussed as appropriate.

5.9   Outcome measures

All measures described below will be taken at baseline (before periodontal treatment) as well as 3 and 6 months after treatment. We will assess standard measures of disease activity that are routinely used in clinical trials of RA, including DAS28 and ACR criteria (ACR20, ACR50, ACR70) [22]. While these composite scores are established outcome measures that are routinely used in RA drug clinical trials, they have several limitations in evaluating the efficacy of periodontal therapy. Firstly, DAS28 as well as ACR criteria include serum concentrations of acute-phase reactants (ESR, CRP) as one of their components. However, in the context of a concomitant inflammatory disease such as periodontitis, a reduction in the acute-phase component of the DAS28 or the ACR criteria afforded by successful periodontal treatment may not reflect a 'true' reduction in disease activity, that will lead to reduced structural damage. Indeed, inflammatory biomarkers have been shown to decrease in response to periodontal therapy in some studies [23] and reductions in serum levels of acute-phase reactants in patients with RA may therefore solely reflect elimination of periodontal inflammation and occur independently of RA disease activity. Secondly, both DAS28 and ACR criteria include patient global assessment of disease activity, which is obviously a highly subjective measure. Because it is impractical to blind the patient with regards to the periodontal intervention, DAS28 and ACR criteria are outcomes particularly susceptible to placebo effects. We therefore propose joint ultrasonography as a sensitive and more objective, non-invasive and relatively inexpensive primary outcome measure.

5.10   Ultrasonography

Ultrasonography is rapidly becoming the tool of choice to assess changes in the joint in response to therapy, based upon high sensitivity to subclinical active joint disease [24], improved reliability versus clinical counts [25], and the ability to predict joint damage using power doppler detection techniques [26]. We propose to use a 12 joint count assessing bilaterally wrist joints and metacarpophalangeal joints for greyscale synovitis and power doppler enhancement. Individual joint scores will be summed
to provide overall ultrasound indexes for greyscale and power doppler. Ultrasound scans will be performed by an experienced operator blinded to participants' clinical or treatment details, using one of the University of Birmingham's two dedicated high resolution ultrasound machines. The proposed scan takes no more than 30 minutes to complete.

5.11   Other outcome measures

Other outcomes measures to be assessed at baseline and 3 and 6 months include: DAS28, ACR20, ACR50, ACR70 (including the components of these composite scores), physical function using the Health Assessment Questionnaire (HAQ), periodontal and general (EQ-5D-5L, PHQ9, MAF), rheumatologic (AIMS2) [27] and oral health related quality of life (OHIP). In addition, venous blood samples will be taken at baseline, 3 months and 6 months, frozen in aliquots and stored for further laboratory analyses.

5.12   Periodontal measures

Periodontal assessments will be made to confirm eligibility and monitor periodontal treatment response. A trained and calibrated examiner, will performfull mouth probing and clinical attachment levels at four sites per tooth.

5.13   Other measures (covariate data)

We will collect baseline data on age, gender, race/ethnicity, socio-economic status (postcode), education, marital status, smoking history, height and weight, comorbidities and concomitant medications, disease duration, ACPA and RF status, background treatment, and joint damage (radiographs of hands and feet).

5.14   Qualitative Interviews

We will conduct semi-structured interviews with patients randomised to either the intervention or control groups, as well as with patients who refused to participate even though they would have been eligible for the study. Data from the first five patients in these groups will be used to design the topic guide for the semi-structured interviews. It is anticipated that questions will be asked in relation to the following areas: oral health maintenance, treatment preferences (dental and medical), access to dental care, priorities/values placed on oral health, quality of life issues, acceptability of the intervention and, if applicable, reasons for non-participation. The interviews will be conducted at Birmingham Dental Hospital, or, for patients unwilling to participate, over the phone. They will be audio recorded and, subsequently, will be fully transcribed. Because of the small sample size to be recruited into this pilot study, we do not propose to use purposive sampling based on predefined population characteristics. Instead, we will sample consecutive patients and conduct the interviews until saturation is reached, which will ensure a broad range of views and yield of the most comprehensive understanding of the subject.

A framework approach to data analysis will be adopted in the manner suggested by Pope et al. [28] A preliminary framework, based on the research questions, will be developed. The transcripts will be read and, following familiarisation with the data, the initial framework will be expanded to reflect themes emerging from the interviews. The data will then be indexed according to the framework and further refined. To guard against bias, the transcripts will be analysed independently by another researcher. Subsequently, consensus will be achieved on emergent themes and issues.

5.15 Statistical considerations

This is a pilot study and no formal sample size calculation is presented. However, this feasibility study will also need to establish that the periodontal treatment as delivered in this study is achieving a minimum standard in terms of periodontal healing (pocket probing depths reduction at 3 and 6 months). A reasonable minimum threshold criterion is to expect an effect size of 1 for reduction of mean probing depth. The feasibility study will have >90% power to detect such an effect size, even allowing for 20% loss to follow-up.

5.16 Analysis Plan

Endpoints to be evaluated will include:
- ultrasound joint scores
- DAS28 and ACR20, ACR50, ACR70
- tender and swollen joint counts
- HAQ,
- OHIP
- AIMS2
- EQ-5D-5L
- PHQ9
- MAF
- ESR,
- hsCRP
- Proportion of patients who reach DAS28 <3.2
- Proportion of patients who receive rescue treatment/upward dose adjustment during study

5.17 Statistical Analysis

Summary statistics will be calculated as appropriate. To test for between group differences at 3 and 6 months, parametric and non-parametric methods will be used as appropriate. For continuous outcomes, differences between groups at 3 and 6 months will be tested using ANCOVA adjusting for baseline. For proportions, relative risks and risk differences will be calculated, and logistic regression adjusting for baseline will be used as appropriate.

6. Patient & Public Involvement

Patient/public involvement will not be a 'stand-alone' activity but rather an integral part of all workpackages. Indeed, the rationale and design of this research have already been discussed with the Patient User Group from Sandwell and West Birmingham Hospitals NHS Trust and two representatives of the group will be members of the steering committee of the study (see letters of support).

Discussions with the Patient User Group have already resulted in changes to the study design. The initial plan was to follow patients for 12 months and use a 'community care' control group. However, members of the Patient User Group felt that the control group should receive specialist periodontal treatment at the end of

the study and the duration of the study (i.e., the 'delay' in treatment for the control group) was reduced to 6 months in response to their concerns. Importantly, this trial duration is still consistent with current recommendations for trials on RA disease activity [17].

Direct patient/public involvement will contribute to:
a.   Initial project development.
b.   Project approval via the NRES system.
c.   Project management
d.   Interpretation of the findings and the development of plan for larger definitive study
e.   Dissemination of the findings of the project.

7.   Project Plan
We anticipate being able to complete this pilot study over 2 years. The project will be delivered in the following three workpackages (WP): preparatory work (WP1), conduct of clinical trial (WP2) and data analysis and interpretation, preparation of reports and dissemination (WP3).

WP1 – preparatory work:
This will include finalization of the protocol and study materials, gaining ethical as well as R&D approval, and recruitment of study personnel.

WP2 – conduct of clinical trial:
This will include screening and recruitment of patients, baseline assessments, randomization and intervention delivery and follow-up assessments.

WP3 – data analysis and dissemination:
This will include statistical analysis, data interpretation, presentation of results and manuscript preparation.

8.   Dissemination of research findings
Dissemination of the results will take place through oral and poster presentations at national and international scientific conferences, and the results will be published in peer-reviewed scientific journals. Data will also be disseminated at internal seminar series at which specialist audiences with both a scientific and clinical background attend.
The Patient User Group and Patient representatives will also provide input and determine on how to best disseminate the results to a wider audience, if appropriate. However, it is important to note that specific dissemination plans will depend on the results of this pilot study and dissemination of preliminary results to a wider audience may not be appropriate.

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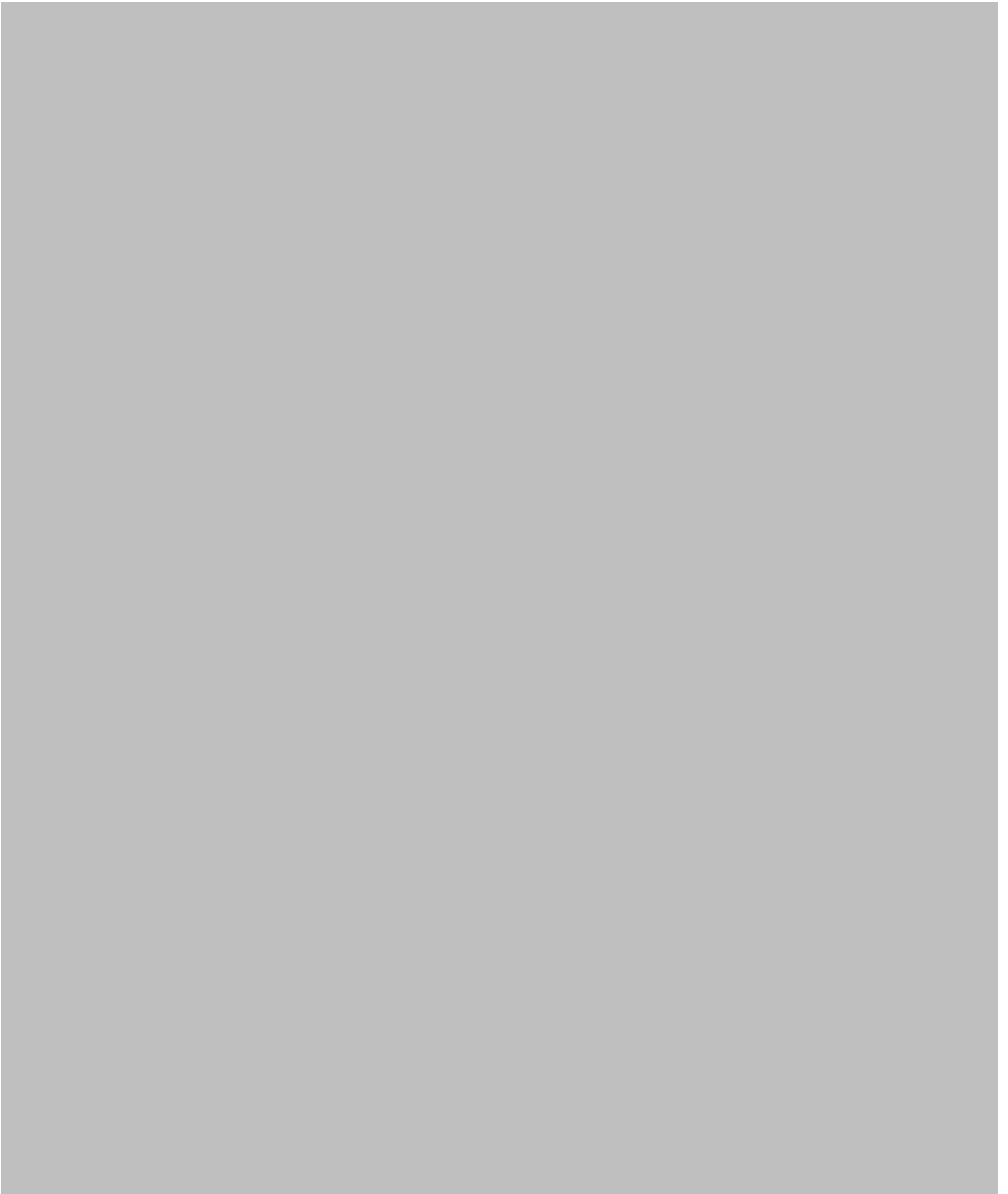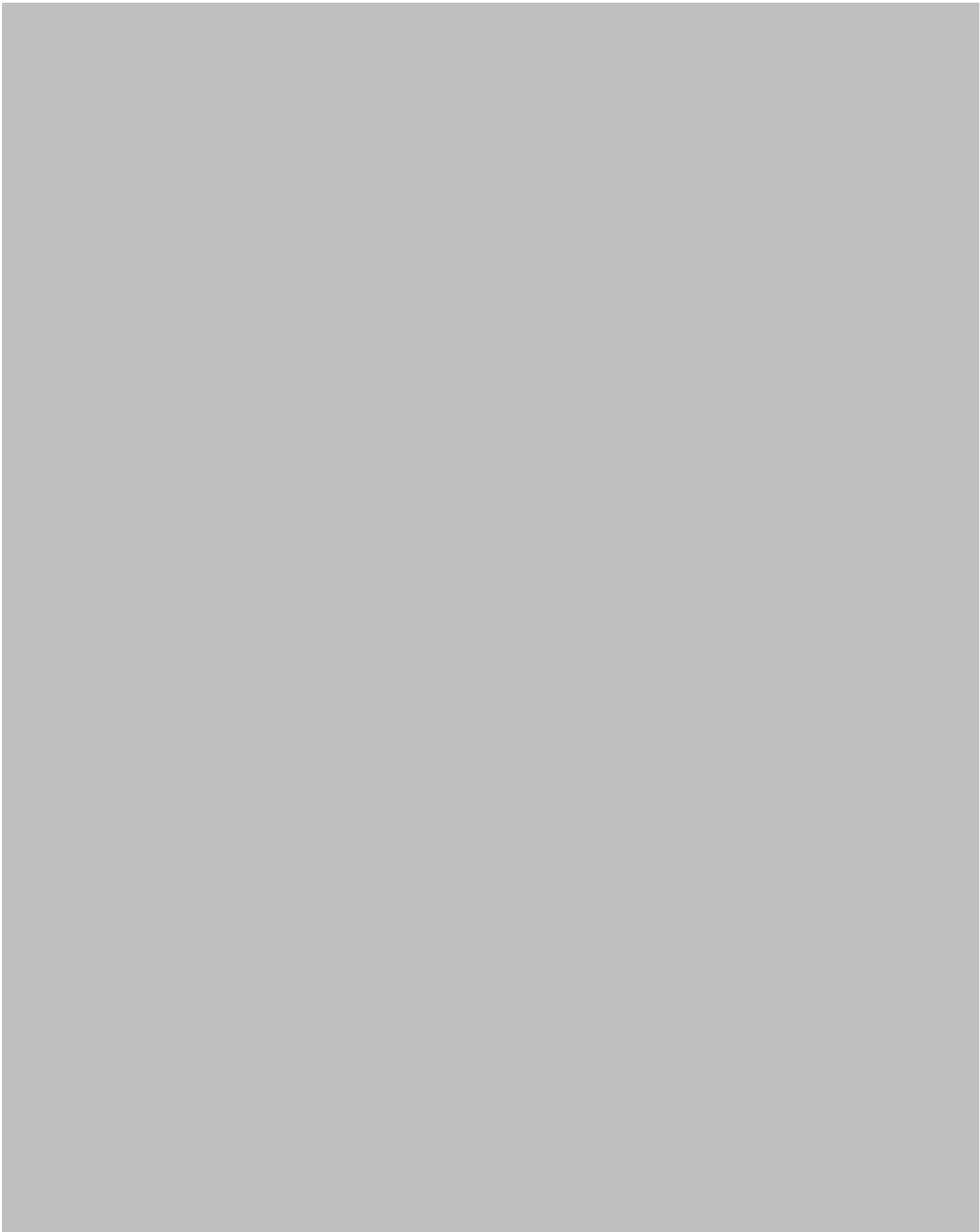
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9 Appendix 2: Ethics Approvals

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10 Appendix 4: Recruitment letter

Queen Elizabeth Hospital **NHS**
Birmingham
Part of University Hospitals Birmingham
NHS Foundation Trust

Name and address

Department of Rheumatology
Queen Elizabeth Hospital
Birmingham
B15 2WD

Date as postmarked

Tel: 0121 627 8314
Fax: 0121 371 6826
http://www.uhb.nhs.uk

Dear Patient,

Re – Invitation to join Research study looking at the link between chronic periodontitis (gum disease) and rheumatoid arthritis

The Rheumatology Department at the Queen Elizabeth Hospital in Birmingham is involved in a research study into the link between gum disease and rheumatoid arthritis. The study is funded by the Department of Health. We are writing to you and other patients on our list that may be suitable to join this study and to help with our research.

To enter this study you must be over 18 years old and have rheumatoid arthritis. The study will involve an examination of your teeth and gums and may also involve treatment of gum disease by a specialist at Birmingham Dental Hospital, if this is appropriate for you.

You do not need to take any new medication to help with this research. You will continue to take your medicines as before. Your participation in our research is entirely voluntary and you may opt out at any time should you choose.

We would be very grateful if you would consider helping with this important research project. In order to express your interest or decline please reply using the attached page and the stamped addressed envelope or contact us on the phone

number or email address below. We will send more detailed information to those who are interested in our research.

Thank you for taking the time to read this.

Yours sincerely,

Dr. Paresh Jobanputra
Consultant Rheumatologist
& Clinical Service Lead

Dr. Simon Bowman
Consultant Rheumatologist

Dr. Andrew Filer
Consultant Rheumatologist

Dr. Elizabeth Justice
Consultant Rheumatologist

Dr. Alison Jordan
Consultant Rheumatologist

Dr. Ben Fisher
Consultant Rheumatologist

Dr. Elizabeth Rankin
Consultant Rheumatologist

Dr. Ben Rhodes
Consultant Rheumatologist

Dr. Paola de Pablo
Consultant Rheumatologist
Clinical Lecturer

Response Form for Arthritis Study (OPERA)
For attention of: [name of study doctor/research nurse]

Please complete this reply slip and return it in the attached envelope or phone the surgery to register your response. Do please note that your reply does not commit you under any obligation whatsoever, and you will have the opportunity to have any questions answered before entering this study.

Name

Address

Date of Birth

Please register your response as follows:

[ ] Yes! Please contact me with further details about this study. I understand that I will be given further information and fully informed before making any decision.

[ ] No, sorry I am not interested in taking part.

Or contact me by telephone on the following number(s).

<< insert phone number >>

11 Appendix 5: Patient Information Sheet (PIS) Screening

Specialist Division
Birmingham Dental Hospital
St Chad's Queensway
Birmingham
B4 6NN

Tel: 0121 466 5000
Fax: 0121 466 5151

Patient Information Sheet SCREENING V1.4, 12/01/2015

Title of study:
Outcomes of Periodontal Therapy in Rheumatoid Arthritis (OPERA, 11/WM/0235)

Invitation to take part

You are being invited to take part in a research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the study?

Chronic periodontitis (gum disease) is a chronic inflammation of the gums around the teeth. This inflammation can ultimately result in loosening and loss of teeth. Gum disease is common in the UK population with about 10-15% of the population suffering from this condition. Recent research has suggested that gum disease is seen more often in patients with rheumatoid arthritis and may also be a factor in the development and progression of this disease. Effective and safe treatments for gum disease exist, and some initial studies suggest that successful treatment of periodontitis may benefit patients with rheumatoid arthritis.

The aim of this study is to study the link between gum disease and rheumatoid arthritis and to find out if treating gum disease can help control disease activity in the joints of patients with rheumatoid arthritis.

Why have I been chosen to take part in the study?

You have been selected because you have rheumatoid arthritis and attend outpatient clinics at one of the centres taking part in this study. If you agree to participate, we will check whether you are eligible to participate in this study according to your rheumatoid health status.

Do I have to take part in the study?

It is your choice as to whether you wish to take part in the study. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form which you will be given a copy of. If you do not want to take part your care will not be affected in any way. If you do take part you are still free to withdraw at any point without giving a reason.

What will happen to me if I take part?

If you decide to take part we will need to record some details about your symptoms and type of arthritis. These assessments will be made with your standard outpatient assessments.

We will then ask you to attend an appointment at the Dental Hospital where a dental specialist will perform an examination of your teeth and gums, which will take about 30 minutes. This is a non-invasive and generally painless procedure routinely performed during a dental examination, although some patients may find it slightly uncomfortable. In addition to these routine dental examinations, we would like to take samples of blood (less than 50ml), dental plaque, gum fluid (a fluid found naturally between your teeth and gums) and saliva. Sampling of plaque, gum fluid and saliva is all non-invasive and has long been established in clinical gum disease research. Your blood, saliva, dental plaque and gum fluid samples will be stored and analysed for markers of inflammation relevant to chronic periodontitis and/or rheumatic disease, including genetic markers. Furthermore, these samples may be used for future, currently unforeseen, medical research projects in the UK and Europe, subject to approval by an Ethics Committee (no personal information would be released from Birmingham).

If the detailed dental examination reveals that you do not have moderate or severe gum disease, your study participation will end and you will continue to receive your standard care for your rheumatoid condition. If however, the dental examination reveals that you have moderate or severe gum disease and meet the study criteria you will then be eligible to continue in the study. If so, a dental specialist will explain to you in more detail the treatment of gum disease and you will have the opportunity to ask any questions. You will be given another patient information sheet which explains the further course of the study and you will again be asked to sign a consent form which you will be given a copy of. If you do not want to continue to take part in the study your care will not be affected in any way. Again, if you do take part you are still free to withdraw at any point without giving a reason.

At any time during the course of the study you may be approached by a health psychologist for an interview about your experience with this study and the study procedures and your experiences and opinions regarding your oral health and healthcare. Topics may include: your experience with this study in terms of acceptability of the study procedures and logistics or your reasons to not participate in this research; your previous experience with visits to the dentist,

barriers to receiving dental care and/or maintaining oral health and your attitude and expectations with regards to dental health. The interviews will last about 20-30 minutes in a private room at the dental hospital. These interviews will be audiotaped and then typed out on paper from the recording. This will be explained in detail to you by the health psychologist and if you agree to be interviewed, you will be asked to sign a separate consent form. You may of course refuse to participate in the interviews and this would not affect your participation in all other aspects of the study.

What do I have to do?
In order to take part in the study you will need to be able to attend appointments both at the Rheumatology outpatient clinic and those at Birmingham Dental Hospital.

Will my taking part in the study be beneficial?
Screening of your gum condition may find undiagnosed gum disease; treatment of such disease is important for your oral health. If you have moderate to severe gum disease and are enrolled in the study, you will receive treatment of the condition in a specialist clinic at Birmingham Dental Hospital.

Will my taking part in this study be kept confidential?
All information given by you and all results obtained will be treated in the strictest confidence. You will be allocated a study number, so your name will not be disclosed to anyone except the clinical people treating you during the study. Using the study number, it will be possible for the researchers to link the results of the research tests back to you as an individual. However, you will never be identified individually in any publications.

Are there any side effects of the treatment?
You may develop a bruise on the arm where the blood is taken; this will settle within a few days.

What are the possible disadvantages and risks of taking part?
Other than the possible side effects described above and the inconvenience caused by the additional time required for the study procedures, there are no disadvantages with participation in this study.

What happens when the research study stops?
You should continue to attend your general dentist for maintenance of your oral health, and you will continue to be reviewed in the outpatient Rheumatology clinic.

What if something goes wrong?
If you are harmed by taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if

you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms will be available to you.

Who is organising or funding the research?
The study is organised by a team of investigators at the University of Birmingham College of Medical and Dental Sciences. The study is funded by the Department of Health via the Research for Patient Benefit Programme of the NHS National Institute for Health Research. Funding is also available from a research grant by the European Union.

Who has reviewed this study?
This study has been reviewed by the funding body as well as by the South Birmingham Research Ethics Committee.

Contact for further information?
If you require any further information please telephone   and ask to speak to Professor Thomas Dietrich.

If you have any concerns about the study and wish to contact someone independent, you may contact the Patient Advice and Liaison Service (PALS) (0121 507 5169 – City Hospital, 0121 371 3280 – Queen Elizabeth Hospital, 0800 917 2855 - Dental Hospital).

A copy of this information sheet and a signed consent form will be given to you to keep.

12 Appendix 6: Informed Consent Form (ICF) Screening

Birmingham Community Healthcare **NHS**

NHS Trust

Consent Form (Version 1.3, 24/NOV/2014, 11/WM/0235)   **Specialist Division**
Birmingham Dental Hospital
St Chad's Queensway

SCREENING

Birmingham
B4 6NN

Title of Project: **Outcomes of Periodontal Therapy in Rheumatoid Arthritis (OPERA)**

Name of Investigator: Professor Thomas Dietrich

Please initial box

1. I agree to take part in this study and confirm that I have read and understood the information sheet **SCREENING**, dated 12/JAN/2015 (Version 1.4) for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason.

3. I understand that the data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data.

4. I agree to have my blood, saliva, dental plaque and gum fluid taken, stored and analysed for research into markers of inflammation, including genetic markers, relevant to chronic periodontitis and/or rheumatic disease.

5. I agree to have my blood, saliva, dental plaque and gum fluid taken, stored and analysed for future, currently unforeseen, medical research projects in the UK and Europe, subject to approval by an Ethics Committee (no personal information would be released from Birmingham).

6. I agree to be contacted in the future regarding consent to future use of my blood, saliva, dental plaque and gum fluid samples.

7. I agree to my general practitioner (GP) and general dental practitioner (GDP) being informed about my participation in this study.

_____   _____   _____
Name   Date   Signature

_____   _____   _____
Investigator   Date   Signature

1 for patient; 1 for site file; 1 for hospital notes

Accessible, Responsive Community Healthcare

INVESTORS IN PEOPLE | Bronze

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13 Appendix 7: Patient Information Sheet (PIS) Treatment

Specialist Division
Birmingham Dental Hospital
St Chad's Queensway
Birmingham
B4 6NN

Tel: 0121 466 5000
Fax: 0121 466 5151

Patient Information Sheet TREATMENT V1.4, 12/01/2014

Title of study:
Outcomes of Periodontal Therapy in Rheumatoid Arthritis (OPERA, 11/WM/0235)

Invitation to take part
You are being invited to continue to take part in this research study. Before you decide, it is important for you to understand why the research is being done and what it will involve. Please take time to read the following information carefully and discuss it with others if you wish. Ask us if there is anything that is not clear or if you would like more information. Take time to decide whether or not you wish to take part. Thank you for reading this.

What is the purpose of the study?
Chronic periodontitis (gum disease) is a chronic inflammation of the gums around the teeth. This inflammation can ultimately result in loosening and loss of teeth. Gum disease is common in the UK population with about 10-15% of the population suffering from this condition. Recent research has suggested that gum disease is seen more often in patients with rheumatoid arthritis and may also be a factor in development and progression of this disease. Effective and safe treatments for gum disease exist, and some initial studies suggest that successful treatment of periodontitis may benefit patients with rheumatoid arthritis.
The aim of this study is to find out if treating gum disease can help control disease activity in the joints of patients with rheumatoid arthritis.

Why have I been chosen to take part in the study?

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You were initially selected because you have rheumatoid arthritis and attend outpatient clinics at one of the centres taking part in this study. During your recent dental examination you have been found to have moderate or severe gum disease (chronic periodontitis).

Do I have to continue to take part in the study?
It is your choice as to whether you wish to continue to take part in the study. If you do decide to take part you will be given this information sheet to keep and be asked to sign a consent form which you will be given a copy of. If you do not want to take part your care will not be affected in any way. If you do take part you are still free to withdraw at any point without giving a reason.

What will happen to me if I take part?
If you decide to take part some details about your symptoms and type of arthritis will need to be updated at 3 and 6 months after your entry into the study. These assessments will be made with your standard outpatient assessments in the Rheumatology clinic.

We will use ultrasound to look at your joints. This will take about 30 minutes and is an entirely harmless procedure. The detailed dental examination and the ultrasound scan will be repeated at 3 and 6 months and will be conducted at the Dental Hospital. If you hadn't had x-rays of your hand and feet within the past 6 months, we would also like to take such x-rays to assess how much damage there is to the joints of your hands and feet.

You will be seen by a dental hygienist who will give you detailed instructions on home cleaning techniques for your teeth. You will then be allocated into one of two groups by a random procedure (similar to the flip of a coin). Both groups will receive standard therapy for gum disease which consists of a thorough 'deep cleaning' of the teeth by the study hygienist with or without local anaesthesia as necessary. One group will have this treatment done immediately; the other group will have treatment deferred for 6 months. However if we find deterioration of your gum condition during this time, treatment of the affected teeth will be provided immediately. Depending on the severity of your gum disease and the number of teeth you have, this treatment may take 2 to 3 visits to complete. The periodontal treatment provided will be a standard treatment which has been routinely used for the treatment of periodontitis for many decades. No surgery or drug treatment will be involved. Following the completion of treatment you will be re-examined 3 and 6 months afterwards. In addition to the treatment procedures and routine dental examinations, we would like to take samples of blood (less than 50ml), dental plaque, gum fluid (a fluid found naturally between your teeth and gums) and saliva at all visits to the Dental Hospital. Sampling of plaque, gum fluid and saliva is all non-invasive and has long been established in clinical gum disease research. We also request permission to take a small biopsy from your inflamed gum tissue during the treatment. This will only be done from sites under local anaesthesia and

will therefore not lead to any additional discomfort. Some samples will be analyzed immediately and some stored for analysis at a later date.

Furthermore, we would like to ask you to complete a series of questionnaires that will assess to what extent your daily life is affected by your oral and general health. The study will finish following the 6 month assessment and completion of periodontal treatment for those patients allocated to the deferred treatment group. Please see the study diagram which summarises the course of the study.

What do I have to do?
In order to take part in the study you will need to be able to attend all appointments both at the Rheumatology outpatient clinic and those at Birmingham Dental Hospital.

Will my taking part in the study be beneficial?
You will receive treatment for your gum disease in a specialist clinic. If indeed treatment of gum disease is beneficial for rheumatoid arthritis (this is what we are trying to find out with this study), then participation in this study may also have a positive impact on your rheumatoid arthritis.

Will my taking part in this study be kept confidential?
All information given by you and all results obtained will be treated in the strictest confidence. You will be allocated a study number, so your name will not be disclosed to anyone except the clinical people treating you during the study. Using the study number, it will be possible for the researchers to link the results of the research tests back to you as an individual. However, you will never be identified individually in any publications.

Are there any side effects of the treatment?
Treatment of gum disease may cause your gums to shrink a little, but these are accepted consequences of managing this disease. Following the treatment, you may also experience some increased sensitivity of your teeth to hot and cold temperatures. This is a temporary side effect and your treating hygienist will be able to advise you on how to minimise it. You may develop a bruise on the arm where the blood is taken; this will settle within a few days.

What are the possible disadvantages and risks of taking part?
Other than the possible side effects described above and the inconvenience caused by the additional time required for the study procedures, there are no disadvantages with participation in this study.

Expenses/Payments
You will not be charged for any treatment costs or any other procedure done as part of the study. If you are eligible and participate in the study we will pay you £50 upon completion of the study.

What happens when the research study stops?
On completion of your treatment you should continue to attend your general dentist for maintenance of your condition, and you will continue to be reviewed in the outpatient Rheumatology clinic.

What if something goes wrong?
If you are harmed by taking part in this study, there are no special compensation arrangements. If you are harmed due to someone's negligence, then you may have grounds for a legal action but you may have to pay for it. Regardless of this, if you wish to complain, or have any concerns about any aspect of the way you have been approached or treated during the course of this study, the normal National Health Service complaints mechanisms will be available to you.

Who is organising or funding the research?
The study is organised by a team of investigators at the University of Birmingham College of Medical and Dental Sciences. The study is funded by the Department of Health via the Research for Patient Benefit Programme of the NHS National Institute for Health Research.
Funding is also available from a research grant by the European Union.

Who has reviewed this study?
This study has been reviewed by the funding body as well as the South Birmingham Research Ethics Committee.

Contact for further information?
If you require any further information please telephone ⬛⬛⬛⬛⬛ and ask to speak to Professor Thomas Dietrich.

If you have any concerns about the study and wish to contact someone independent, you may contact the Patient Advice and Liaison Service (PALS) (0121 507 5169 – City Hospital, 0121 371 3280 – Queen Elizabeth Hospital, 0800 917 2855 - Dental Hospital).

A copy of this information sheet and a signed consent form will be given to you to keep.

14 Appendix 8: Informed Consent Form (ICF) Treatment

Birmingham Community Healthcare **NHS**
NHS Trust

Consent Form (Version 1.3, 24/NOV/2014, 11/WM/0235) **Specialist Division**
Birmingham Dental Hospital
St Chad's Queensway
Birmingham
B4 6NN

TREATMENT

Title of Project: **Outcomes of Periodontal Therapy in Rheumatoid Arthritis (OPERA)**

Name of Investigator: Professor Thomas Dietrich

Please initial box

1. I agree to take part in this study and confirm that I have read and understood the information sheet **TREATMENT**, dated 12/JAN/2015 (Version 1.4) for the above study and have had the opportunity to ask questions.

2. I understand that my participation is voluntary and that I am free to withdraw at any time, without giving any reason.

3. I understand that the data collected during the study may be looked at by individuals from regulatory authorities or from the NHS Trust where it is relevant to my taking part in this research. I give permission for these individuals to have access to my data.

4. I agree to have my blood, saliva, dental plaque, gum fluid and gum biopsy taken, stored and analysed for research into markers of inflammation, including genetic markers, relevant to chronic periodontitis and/or rheumatic disease.

5. I agree to have my blood, saliva, dental plaque and gum fluid and gum samples taken, stored and analysed for future, currently unforeseen, medical research projects in the UK and Europe, subject to approval by an Ethics Committee (no personal information would be released from Birmingham).

6. I agree to be contacted in the future regarding consent to future use of my blood, saliva, dental plaque, gum fluid and gum samples.

7. I agree to my general practitioner (GP) and general dental practitioner (GDP) being informed about my participation in this study.

_____   _____   _____
Name   Date   Signature

_____   _____   _____
Investigator   Date   Signature

1 for patient; 1 for site file; 1 for hospital notes

Accessible, Responsive Community Healthcare

INVESTORS IN PEOPLE | Bronze

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15 Appendix 9: Case report form

INTERVIEW

_____

Patient screening number

Patient initials:

Alcohol

Alcohol (Units/week)

How often do you have a drink containing alcohol?

❑ Never

❑ Monthly or less

❑ 2-4 times a month

❑ 2-3 times a week

❑ 4 or more times a week

Smoking

Have you ever smoked?

❑ *Yes*

❑ *No*

If yes, have you smoked more than 100 cigarrettes in your life?

❑ *Yes*

❑ *No*

If yes:

#cigs/day

If former/current: age started

If former: age stopped

Screening number

GENERAL EXAMINATION

_____

Height (cm-only at initial visit)

[ ]

Weight (kg)

[ ]

Sistolic BP (mmHg)

[ ]

Diastolic BP (mm Hg)

[ ]

Blood taken   ❑   ❑   Time blood taken
        Yes   _No_

[ ]

GCF   ❑   ❑
   Yes   _No_

GCF 1-upper right premolar	GCF 2-upper right molar	GCF 3-upper left premolar	GCF 4-upper left molar
[ ]	[ ]	[ ]	[ ]

Saliva sample taken   ❑   ❑
        Yes   _No_

Time saliva

❑ _5 min_

❑ _10 min_

Volume (ml) saliva

[ ]

FLORIDA PROBING   ❑   ❑
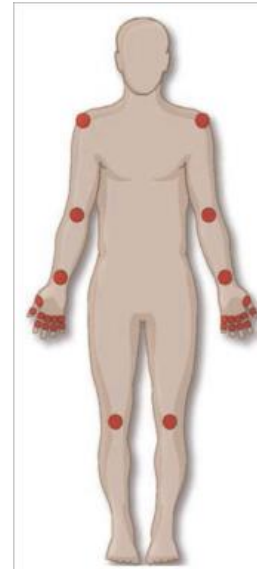   _Yes_   _No_

DAS 28   ❑   ❑
        Yes   _No_

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_____

DAS 28

DAS 28

	LEFT-tender	LEFT-swolen	RIGHT-tender	RIGHT-swolen
Shoulder	❑	❑	❑	❑
Elbow	❑	❑	❑	❑
Wrist	❑	❑	❑	❑
MCP 1	❑	❑	❑	❑
MCP2	❑	❑	❑	❑
MCP 4	❑	❑	❑	❑
MCP 5	❑	❑	❑	❑
PIP 1	❑	❑	❑	❑
PIP 2	❑	❑	❑	❑
PIP 3	❑	❑	❑	❑
PIP 4	❑	❑	❑	❑
PIP 5	❑	❑	❑	❑
Knee	❑	❑	❑	❑

Total tender

Total swolen

Patient Global Assessment of Disease Activity

CONSIDERING ALL THE WAYS YOUR ARTHITHIS AFFECTS YOU, RATE HOW WELL YOU
ARE DOING ON THE FOLLOWING SCALE:

VERY	0	0.5	1	1.5	2	2.5	3	3.5	4	4.5	5	5.5	6	6.5	7	7.5	8	8.5	9	9.5	10	VERY
WELL	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	❑	POOR

_____

How to score de DAS

Tender joint score (0-28)	
Swolen joint score (0-28)	
ESR	
VAS disease activity (0-100mm)	
TOTAL SCORE	

Have you been taking DMARDs since > or = 3 months ago?

❑ *yes*

❑ *no*

Has the dose been stable for > or = 2 months?

❑ *yes*

❑ *no*

Eligibility

	Yes	*No*
DAS 28 > or = 3,2	❑	❑
DAS 28 > 5,1 only if patient on biologics or patient unwilling to take biologics	❑	❑
DMARD > or = 3 months	❑	❑
DMARD stable dose > or = 2 months	❑	❑
CAL > or = 4 mm on at least 2 adjacent teeth	❑	❑
Cumulative probing depth > or = 40 mm	❑	❑
ELIGIBLE	❑	❑

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16 Appendix 10: Euro-Quol

17 Appendix 11: Patient Health Questionnaire (PHQ-9)

OPERA

Screening number

_____

Patient Health Questionnaire (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems?

	Not at all	Several days	More than half the days	Nearly every day
Little interest or pleasure in doing things	☐	☐	☐	☐
Feeling down, depressed, or hopeless	☐	☐	☐	☐
Trouble falling or staying asleep, or sleeping too much	☐	☐	☐	☐
Feeling tired or having little energy	☐	☐	☐	☐
Poor appetite or overeating	☐	☐	☐	☐
Feeling bad about yourself or that you are a failure or have let yourself or your family down	☐	☐	☐	☐
Trouble concentrating on things, such as reading the newspaper or watching television	☐	☐	☐	☐
Moving or speaking so slowly that other people could have noticed. Or the opposite being so figety or restless that you have been moving around a lot more than usual	☐	☐	☐	☐
Thoughts that you would be better off dead, or of hurting yourself	☐	☐	☐	☐

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all	Somewhat difficult	Very difficult	Extremely difficult
☐	☐	☐	☐

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18 Appendix 12: Oral Health Impact Profile (OHIP)

OPERA

Pg. 14/16

20 Appendix 14: The ultrasound grading sheet used for OPERA

Date:

Indication: **OPERA**

Sonographer:

Patient Details/Label

WRISTS

UC		IC		RC			RC		IC		UC	
GS	PD	GS	PD	GS	PD		GS	PD	GS	PD	GS	PD

| M5 GS | M5 PD | | | | | | | | | | | M5 GS | M5 PD |

R **L**

| M4 GS | M4 PD |
| M3 GS | M3 PD |

MC PJs

| M4 GS | M4 PD |
| M3 GS | M3 PD |

| P5 GS | P5 PD | | M2 GS | M2 PD | | M1 GS | RM1 PD | | M1 GS | M1 PD | | M2 GS | M2 PD | | P5 GS | P5 PD |

| P4 GS | P4 PD | | P4 GS | P4 PD |

| P3 GS | P3 PD | PI PJs | P3 GS | P3 PD |

| P2 GS | P2 PD | | P1 GS | P1 PD | | P1 GS | P1 PD | | P2 GS | P2 PD |
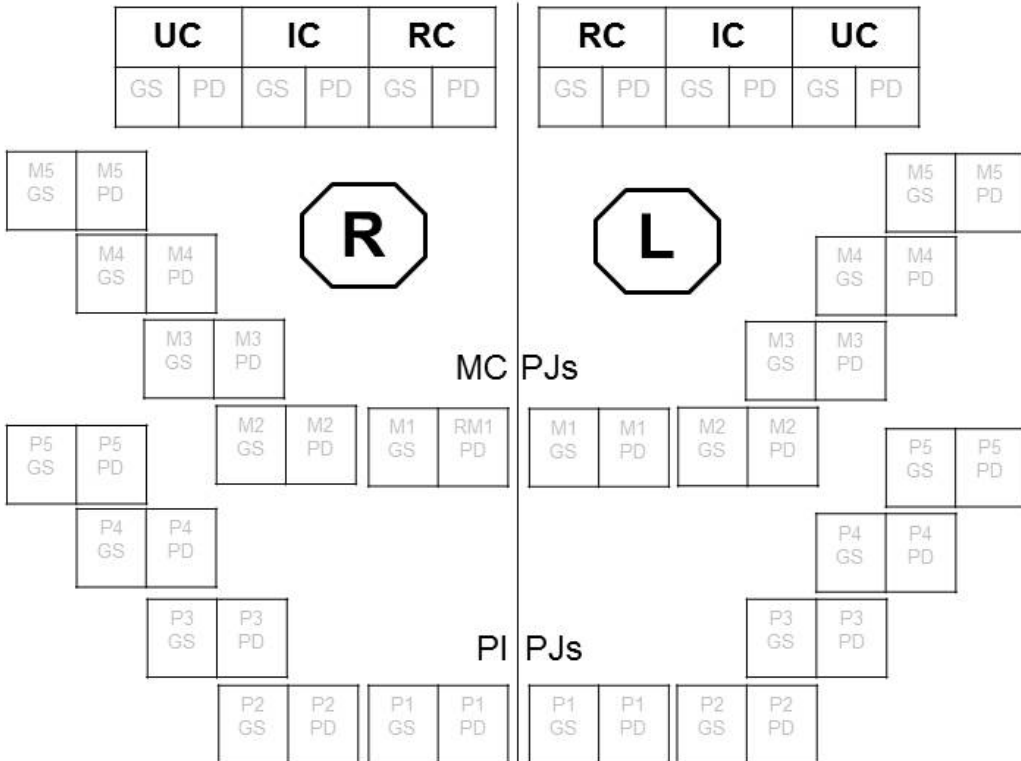
21 Appendix 15: Example from the Qualitative Data Analysis

Respodent	History	Effect of RA on QoL
Pt 1	Diagnosed in 1997, aggressive start	Affecting capacity of take care of own child as mother
Delayed treatment	Q It started in my feet. (p4)	QQQ Everyday things that I would have done without blinking an eye just became totally impossible to do because I had no grip in my hands, no strength then to actually get myself up in the bed (p3)
Female, 60	QQ I remember going to pick my son up from school and walking up high street and just with tears rolling down my face because I was in such pain and I am not a baby when it comes to pain, I think I have got quite a high pain threshold, but it was just I had never known anything like it and then it just got worse from there …. (p5)	QQQ basically accepting that your life is not going to be what it was. For instance, walking a certain distance, or going out for walks in the park which are things we used to do (p3)
	GP didn't recognise the disease imediately (p5)	QQQ I'd spend hours and hours in the kitchen cooking, I can't do that anymore (p4)
	QQ, "Oh my God, what's happening to me". All I could move was my eyes, couldn't move anything else. I just went into a complete erm, I don't know what you would call it. It's like when I do get down the side, I do get where I lock where I go into really bad pain, I get a flare-up and I will lock all down the side.(p5)	Q I have to accept that there is not a lot, you know, physically, I am not capable of doing an awful lot. (p5)
Pt 2	Started when the pt was 65 or 75 (p1)	Pt complains that because of RA, cannot use his hands properly (p1)

22 Appendix 16: Topic guide for the qualitative interviews

22.1 Initial topic guide framework

The initial topic guide framework was composed of the following topics:

22.1.1 Introduction

- Introduction about the purposes of the study

- Explanation about confidentiality issues and tape recording

22.1.2 Rheumatoid arthritis and systemic health

- Discussion regarding the way that rheumatoid arthritis affects the patient's quality of life

- The patients were asked to describe their top 5 health priorities?

22.1.3 Periodontitis and oral health

- The patients were asked to describe their dental health

- The patients were asked to describe any steps they take to maintain their dental health

- The patients were asked to describe their cleaning/flossing habits

- The patients were asked to describe the frequency of their oral hygiene habits

- The patients were asked to describe if they experienced any influence of their rheumatoid arthritis on their dental health

- The patients were asked to describe their relationship with their general dental practitioner

22.1.4 The Study

- The patients were asked to describe the reasons why they decided to participate or not participate in the study

- The patients that took part in the study, were asked to describe their experiences regarding the screening visit:

- What represented a positive experience

- What factors they considered positive or encouraging for a dental visit, based on their previous experiences with their dental care provider

  o Surgery

  o Staff

  o Modern equipment

  o Communication skills

- The patients were asked to describe if they had any negative experiences in the past with their dental care provider

- What they liked or disliked about the study

- The patients were asked to imagine what they would do differently if they were in charge with organizing the study

22.1.5 Factors influencing participation in the research project

- The patients were asked to describe the factors that encouraged or would encourage them to participate in the study

  o Pain free assessments

  o Gender of the dentist

- The patients were asked to describe the barriers that they felt that would hinder their participation in the study

- If they had any (dental) anxiety related issues

- If they encountered any barriers to care

- Language or cultural difficulties

- Fear or embarrassment

- The patients were asked to describe their dental anxiety or fear related experiences

- The patients were asked to describe types/cause/experiences

- Specific fears

- The patients were asked to talk about the onset of these fears

- Coping strategies

- Any history of non-dental anxieties

- The patients were asked to talk about the removal of barriers

- What would encourage better attendance in their opinion

- What action should the profession or the government take to promote better attendance in their opinion

22.2 The final topic framework.

The first three topics: Introduction, Rheumatoid arthritis and systemic health and Periodontitis and oral health did not suffer significant changes

22.2.1 The Study

The following topics emerged and were added to the final topic guide:

- The patients described how they would feel being in the control group and getting treatment with a delay.

- The patients discussed about the length of time for which they would agree to be delayed and not seek treatment elsewhere

22.2.2 Factors influencing participation in the research project

The following topics emerged and were added to the final topic guide:

- The patients described how financial compensation would encourage participation in the project.

- The patients described how often and how much would represent a fair amount of financial compensation for study participation.

- What types of outcomes would the patients find interesting to enhance study participation

23 Appendix 15: Standard operating procedures for biological sample collection

SOP - OPERA

1. ACPA - QE
- Check on Patient Portal in QE/City Hospital if the patient has already the ACPA
- If not, request them to be done after the patient signs the consent form

All the following samples are collected at screening visit and for the randomized

patients, it is repeated at 3 months and 6 months follow-up

2. ESR – QE
- Check on Patient Portal in QE/City Hospital if the patient has any recent ESR done
- If not, request them to be done after the patient signs the consent form

3. Venous blood samples in frozen in aliquots
- **<u>Clinic</u>**
- A qualified phlebotomist will collect the blood samples, during the screening and the follow-up visits
- Quantity ≤ 50 ml in 4 red + 4 green tubes

- **<u>Lab:</u>**
- Prepare tubes (Star Lab 1.5 ml (E1415-2227) screw top tubes – red/white (E1480-0304) top for serum, green/white (E1480-0302) for plasma) – Label with sample name, visit number and type (cryo stickers provided).
- Fill in form with Date, patient number and visit, sample type.
- Receive bloods – fill out time in form and in comments box fill out how many vials you received
- Centrifuge (2680rpm at 4 degrees for 30mins) – this is usually on setting 1 – fill in form with time [NB serum may need to be left to clot]

- Remove tubes without disrupting the separation.
- Aliquots of 1.5 ml (2 x750ul per tube)
- Keep the plasma packed blood sediment for the DNA isolation (see below)
- Put samples in the appropriate OPERA box order serum, plasma, saliva, DNA
- add sticker or write on to the top of box
- Fill out form to show where the samples are stored in the box plan
- Return all paperwork back to the purple OPERA folder

- **DNA**
- Prepare tubes (Star Lab 1.5 ml screw top tubes – Amber with lilac top) – Label with sample name, visit number and type (cryo stickers provided). Pre prepare in molecular lab hood with 500ul of trireagent.
- Fill in form with Date, patient number and visit, sample type.
- PEG300 located in blood spill kit. Double glove and Face Mask for this procedure.
- Collect pre-prepared tube from flammable cupboard in molecular biology lab, ensuring it stays upright. – If at all concerned, replace tube and use another.
- Return to main lab and place in rack
- Label tubes
- Aliquot 500ul of blood sediment from the green plasma tubes into the trizol tubes, replace cap tightly.
- Invert to mix 5 times
- put into -80 freezer – time on form

4. **GCF sample**
   - **Clinic**
   - Sampling with Periopaper strips
   - Unwrap sterile set of Periopapers (n=16) and mount on holder provided. Take care not to touch paper section of strips (contamination occurs).
   - Set holder down on bracket top.
   - Isolate site to be sampled carefully with sulcus cotton rolls and saliva ejector.
   - Blow air from triple syringe x 5 blasts buccal and palatal/lingual. The direction of the blast should be from gingivae to occlusal surface, i.e. away from gingival crevice and not into the crevice.
   - Check interproximal contacts to ensure they are dry. If not, re-dry interproximal areas as above.
   - Pull Periopaper from holder using college tweezers holding the orange section only. Take care not to touch adjacent strips on the holder.

- Insert the paper portion of the strip so its leading edge is parallel to the line of the gingival margin, try not to bend the strip.
- Insert until gentle resistance is felt and guard strip from cheek/lip contact or contamination during collection (patient must NOT speak).
- The entire leading edge of the strip should enter the crevice, i.e. not just a corner.
- Time for 30-seconds and remove.
- NB. If the strip comes out during sampling, it is often not possible to re-sit it.
- If failure occurs sampling a site, it cannot be re-sampled, the site is lost.
- Blood contamination may invalidate the sample, depending on what is being analysed.
- If there is doubt about saliva contamination, note "? saliva contamination" on CRF.

- **Lab**
- Prepare tubes (Star Lab 1.5 ml amber tubes with yellow top (E1480-0306) – Label with sample name, visit number and type (cryo stickers provided).
- Fill in form with Date, patient number and visit, sample type.
- Receive GCF samples – fill out time in form
- Samples are received on liquid nitrogen, remove from flask and put into -80 freezer – time on form

5. **Microbiological plaque sample**
   - **Clinic**
   - Sample plaque from the 6 deepest interproximal sites (a site is defined as the mesial or distal interproximal space, i.e., no differentiation is made between ml/mb or dl/db sites). These sites should be as distant as possible from each other, one per sextant, if possible.
   - Once representative teeth have been identified, they should be isolated using cotton wools rolls and teeth air dried
   - Subgingival plaque is collected using hand instruments
   - Confirm cryotube/buffer
   - Samples to be stored in a -80°C freezer. (Store grouping samples of the same subject no.)
   - Batch send to Birmingham Dental Hospital, marked FAO Prof Iain Chapple/Prof Thomas Dietrich, on study completion.

   - **Lab**
   - Prepare tubes (Eppendorffs containing 1ml tris EDTA (pH7.4 from Sigma 93302-500ml) – located in Gamma fridge (cryo stickers provided).
   - Fill in form with Date, patient number and visit, sample type.
   - Receive Plaque sample – fill out time in form
   - Samples are received on ice, remove and put into -80 freezer – time on form

6. **Saliva sample**
   - **Clinic**
   - Ask patient if they have followed pre-sampling instructions with respect to eating, drinking, smoking and brushing teeth prior to sampling appointment.
   - Instruct the patient to rinse mouth with sterile water to remove food residue before sample collection. Wait at least 10 minutes after rinsing before collecting saliva to avoid sample dilution.
   - Give the patient the sterile saliva sampling marble.
   - Label the saliva sample tube (graduated Falcon tube) with subject no. study time-point, date and time.
   - Remove lid from the saliva sample tube and place saliva sampling funnel into the saliva sample tube.
   - Place the combination of the saliva sampling funnel and the saliva sample tube into a cup of ice. Give to the patient to hold.
   - Instruct the patient to place a sterile marble in their mouth and continually roll it around for 5 minutes.
   - Instruct the patient to retain the marble in their mouth while expectorating the resulting saliva.
   - Time the patient for 5 minutes and ensure that a minimum of 1.0ml of saliva has been collected.
   - If 1.0ml of saliva has not been collected in 5 minutes then have the patient continue until 1.0ml has been collected.
   - Record the time it took to reach 1.0ml
   - If the patient accidentally spits the marble into the funnel, they can retrieve it with their fingers and replace in it their mouths.
   - Take the apparatus from the patient. Remove the funnel. Leaving the sample tube in the cup of ice, place the lid on.
   - Take the saliva sample to the laboratory.
   - Record total volume. Calculate flow rate (ml/min).

   - **Lab**
   - Prepare tubes (Star Lab 1.5 ml screw top tubes – Amber with blue and white (E1480-0304) top) – Label with sample name, visit number and type (cryo stickers provided).
   - Fill in form with Date, patient number and visit, sample type.
   - Receive saliva – enter time received on form and approx. volume.
   - Centrifuge (2470rpm at 4 degrees for 10mins) – this is usually on setting 3 (using centrifuge 3) – fill in form with time – this will need to be balanced.
   - Remove tubes without disrupting the separation.
   - Remove pellet and store in the tube labelled – pellet.
   - Aliquots of 1.5 mls (2 x750ul per tube) – time on form
   - Snap freeze – time on form
   - Put into -80 freezer – time on form

7. PD

- A calibrated examiner will perform full mouth probing using a manual constant force probe UB-CF-15
- 4 sites on each tooth (except 3rd molars): mb, db, ml, dl
- Record at each site recession, pocket depth and BOP
- BOP is recorded at the end of probing each quadrant

8. RA

DAS28

- A calibrated examiner will perform Disease Activity Score in 28 Joints (DAS28).
- The examiner is going to apply a constant pressure on each of the 28 joints in order to assess swelling and tenderness
- The joints are bilaterally: MCP 1-5, PIP 1-5, wrist, elbow, shoulder and knees
- For each tender and each swollen joint, a point is given
- The patient is offered a visual analogue scale (VAS) and asked to assess the level of pain that was experienced due to RA in the past week
- The DAS28 is calculated using the database created by Naomi, imputing the total number of swollen and tender joints, the VAS score and the patients most recent ESR (not older than 2 weeks)

Ultrasound

- A calibrated examiner for the patients' randomization group allocation (treatment or control) will perform MSK Ultrasound on all the randomized patients using the Philips iU22 ultrasound machine from the BDH Radiology Department
- The machine is placed in a dark room, with no natural light. Lights are turned off and the patients screening number is inserted in the menu as well as the specification of baseline, 3 months FU or 6 months FU
- Aquasonic® 100 Ultrasound Transmission Gel is applied on the patient's joints. Standard longitudinal views are recorded for greyscale and power-doppler on the following joints: Wrist (intercarpal and ulnar-carpal), MCP 1-5, MTP 2-5
- The images are graded on a grading sheet with scores from 0 to 3 in terms of synovitis
- The images are saved both on the ultrasound machine and on the university servers.

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