Protocol Title : A **R**andomised, open labelled study in anti-TNFa inadequate responders to investigate the mechanisms for **R**esponse - **R**esistance to **Rituximab** versus Tocilizumab in RA (R4-RA)

Version: **9.0**

EudraCT reference: **2012-002535-28**

MREC reference: **12/WA/0307**

ISRCTN number: **ISRCTN97443826**

Dated: **30/10/2017**

TITLE OF THE PROTOCOL:

Developing a novel, biopsy-based diagnostic for patient stratification: "A **R**andomised, open labelled study in anti-TNFa inadequate responders to investigate the mechanisms for **R**esponse - **R**esistance to **Rituximab** versus Tocilizumab in RA".

Short title/Acronym: R4-RA

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REC reference: **12/WA/0307**

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Chief Investigator Agreement Page

The clinical study as detailed within this research protocol **(Version9.0, dated30/Oct/2017)** or any subsequent amendments, involves the use of an investigational medicinal product and will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996), Principles of ICH-GCP, and the current regulatory requirements, as detailed in the Medicines for Human Use (Clinical Trials) Regulations 2004 (UK S.I. 2004/1031) and any subsequent amendments of the clinical trial regulations.

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Statistician Agreement Page

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STUDY SUMMARY/SYNOPSIS

TITLE	Developing a novel, biopsy-based diagnostic for patient stratification: "A **R**andomised, open labelled studyin anti-TNFa inadequate responders to investigate the mechanisms for **R**esponse - **R**esistance to **Rituximab** versus Tocilizumab in RA (R4-RA)".
SHORT TITLE	R4-RA
Protocol Version Number and Date	Protocol V9.0 30/10/2017
Methodology	Type of study: open-label, randomised controlled clinical trial, multi-centre, multi-country
Total Study Duration	5 years
Objectives	This study will aim to develop a diagnostic tool (immunohistochemical analysis of synovial tissue) for patient stratification into responsive/non-responsive categories with respect to Rituximab therapy in patients who have had an inadequate response to anti-TNF therapy. Specifically, can a diagnostic synovial biopsy showing a B-cell "rich/poor pathotype" define specific disease responsive/resistant subsets for patient stratification and help rationalize biologic drug choice.
Phase of the Trial	Phase IV study
Number of Subjects/Patients	At least 86 B-cell poor and at least 51-B-cell rich patients. When we have recruited this number of B cell poor and B cell rich patients, it is estimated that we will have 8 Germinal Centre patients. In addition, the total sample size has been increased by 10% to account for the unknown pathotype. It is therefore estimated that we will need approximately 160 patients to achieve 90% power. Recruitment will stop in Dec 2017 or once we have achieved both minima as above, whichever comes first.

Main Inclusion Criteria	Patients will be recruited with active RA: 1. Patients who have failed anti-TNF therapy (inadequate responders – ir). Note: this includes patients that have failed anti-TNF therapy because of reactions. 2. Who are eligible for Rituximab therapy according to UK NICE guidelines* 3. Patients should be receiving a stable dose Methotrexate for at least 4 weeks prior to biopsy visit. 4. 2010 ACR / EULAR Rheumatoid Arthritis classification criteria for a diagnosis of Rheumatoid Arthritis. 5. 18 years of age or over 6. Patient must be capable of giving informed consent 7. Willingness and ability to comply with scheduled visits, treatment plans and laboratory tests and other study procedures *See page 18 for UK NICE guidelines extract.
Statistical Methodology and Analysis	For the randomized comparison of Rituximab versus Tocilizumab in B-cell poor patients, the primary endpoint will be analysed (by intent to treat) using the chi-squared test for the difference between two proportions. For non-randomised comparisons between subgroups identified by B-cells in synovial biopsies, we will use the Fisher exact test comparing response to Rituximab in B-cell poor patients compared to B-cell rich. The definition of B-cell status will be clearly defined before the start of the trial. A test of interaction between treatment and B-cell status (rich versus poor, excluding germinal centre) will be based on a likelihood ratio tests between nested logistic regression models.

Glossary of Terms and Abbreviations

AE	Adverse Event
AR	Adverse Reaction
ASR	Annual Safety Report
CA	Competent Authority
CI	Chief Investigator
CRF	Case Report Form
CRO	Contract Research Organisation
CTA	Clinical Trial Authorisation
CTIMP	Clinical Trial of Investigational Medicinal Product
DMARD	Disease Modifying Anti-Rheumatic Drug
DMC	Data Monitoring Committee
EC	European Commission
EMEA	European Medicines Agency
EU	European Union
EUCTD	European Clinical Trials Directive
EudraCT	European Union Drug Regulating Authorities Clinical Trials
EudraVIGILANCE	European Union Drug Regulating Authorities Pharmacovigilance
GAfREC	Governance Arrangements for NHS Research Ethics Committees
GCP	Good Clinical Practice
GMP	Good Manufacturing Practice
IB	Investigator Brochure
ICF	Informed Consent Form
IMP	Investigational Medicinal Product
IMPD	Investigational Medicinal Product Dossier
ISRCTN	International Standard Randomised Controlled Trial Number
JRMO	Joint Research and Management Office
MA	Marketing Authorisation
MHRA	Medicines and Healthcare products Regulatory Agency
MS	Member State
Main REC	Main Research Ethics Committee
NHS R&D	National Health Service Research & Development
PI	Principle Investigator
QA	Quality Assurance
QC	Quality Control
QP	Qualified Person for release of trial drug
Participant	An individual who takes part in a clinical trial
RCT	Randomised Controlled Trial
REC	Research Ethics Committee
SAE	Serious Adverse Event
SAR	Serious Adverse Reaction
SDV	Source Document Verification
SmPC	Summary of Product Characteristics
SOP	Standard Operating Procedure
SSA	Site Specific Assessment
SUSAR	Suspected Unexpected Serious Adverse Reaction
TMG	Trial Management Group
TSC	Trial Steering Committee
US	Ultrasound

Contents

1 INTRODUCTION

1.1 Background

Rheumatoid arthritis (RA) is one of the most important chronic inflammatory disorders in the UK. The diagnosis of RA leads to considerable morbidity and an increased mortality[1, 2]. According to the National Audit Office (2009 - http://www.nao.org.uk/) there are 26,000 new cases of RA each year with 582,000 prevalent cases in England. 45% of these people are of working age and within 1 year of diagnosis 30% are unemployed. RA is characterized by a symmetrical, erosive polyarthritis, resulting from chronic synovitis, and the presence of circulating autoantibodies such as rheumatoid factor (RF) and anti-cyclic citrullinated peptide (ACPA), strongly suggesting an autoimmune pathogenesis. Although biological therapies have revolutionized the treatment of RA, a sizable group of patients (30-40%) are "resistant"[3, 4].

Recently there has been a greater understanding of the importance of B cells in driving the inflammatory processes involved in RA. B cells may drive synovial inflammation by production of autoantibodies, acting as effective antigen-presenting cells and may promote synovial inflammation by producing pro-inflammatory cytokines[5]. Thus, depletion of B cells could interfere with important mechanisms involved in the perpetuation of the inflammatory response in RA. Rituximab is a chimeric monoclonal antibody directed against the CD20 antigen expressed by B cells, has been approved by the US Food and Drug Administration and by the European Medicines Agency in Europe for the treatment of patients with RA who have had an inadequate response (ir) or were intolerant to tumour necrosis factor alpha (TNF) inhibitors. Current evidence on the efficacy of Rituximab relates primarily to rheumatoid factor positive patients, although even within this population clinical responses are heterogeneous with only 60% achieving an ACR20 response at 6 months[6, 7]. Recent synovial-based studies suggest that the heterogeneous clinical response may in part be explained by variable B cell depletion within the synovial tissue rather than simply in the peripheral blood[8-10]. A growing body of evidence would suggest that a more rational approach to Rituximab therapy and a stratified approach to patients may be required[11-13]. Despite this, NICE guidelines have recommended that all patients with inadequate response to anti-TNF therapy should receive Rituximab (NICE, http://www.nice.org.uk/CG79). A "blind" implementation of these guidelines will result in many patients, unlikely to respond, receiving a B Cell depleting agent with the associated risks with none of the potential benefits. A tailored approach to this intervention with patient stratification is required to better identify both responders and non-responders. In this proposed study we will test the hypothesis that the presence or absence of B cells and B cell-associated signatures within the joint will enrich for response/non-response to the B cell depleting agent Rituximab. We also hypothesize that in patients with a B-cell poor synovial biopsy, alternative biologics such as the IL-6 receptor blocker Tocilizumab will be more effective. This study is considered a type A clinical study according to MHRA risk.

1.2 Investigational Medicinal Products

N.B. Information based on SmPC data current as of September 2012.

1.2.1 Rituximab

Within the remit of this study Rituximab is being used in accordance with its UK licence. Rituximab is a chimeric antibody consisting of a human immunoglobulin G1 (IgG1) kappa constant region with a variable region derived from a murine anti-CD20 antibody. Rituximab selectively targets CD20, a cell surface antigen that is uniquely expressed on a subset of B cells during the maturation process. Rituximab has a high binding affinity for the CD20 antigen, with specificity for the CD20 antigen residing in the variable murine regions. This represents a novel biological strategy for the treatment of rheumatoid arthritis (RA) compared with traditional disease-modifying anti-rheumatic drugs or tumour necrosis factor (TNF) inhibitors. Rituximab can disrupt a number of different events in the inflammatory pocess owing to the central role and multiple actions of B cells in the pathogenesis of RA. The synovial fluid of a joint affected by RA contains an abundance of B cells, and it is now recognised that the B lymphocyte plays three key roles in the pathogenesis of RA: antigen presentation leading to T cell activation, autoantibody production and cytokine production

Rituximab in combination with methotrexate is licensed for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to or intolerance of other DMARDs, including one or more tumour necrosis factor α (TNF-α) inhibitor therapies.

Pharmacokinetic properties

Rituximab binds specifically to the transmembrane antigen, CD20, a non-glycosylated phosphoprotein, located on pre-B and mature B lymphocytes. CD20 is found on both normal and malignant B cells, but not on haematopoietic stem cells, pro-B cells, normal plasma cells or other normal tissue. This antigen does not internalise upon antibody binding and is not shed from the cell surface. CD20 does not circulate in the plasma as a free antigen and, thus, does not compete for antibody binding. Peripheral B cell counts declined below normal following completion of the first dose of Rituximab. In rheumatoid arthritis patients, immediate depletion of B cells in the peripheral blood was observed following two infusions of 1000 mg Rituximab separated by a 14 day interval. Peripheral blood B cell counts begin to increase from week 24 and evidence for repopulation is observed in the majority of patients by week 40, whether Rituximab was administered as monotherapy or in combination with methotrexate. Following two intravenous infusions of Rituximab at a dose of 1000 mg, two weeks apart, the mean terminal half-life was 20.8 days (range, 8.58 to 35.9 days), mean systemic clearance was 0.23 l/day (range, 0.091 to 0.67 l/day), and mean steady-state distribution volume was 4.6 l (range, 1.7 to 7.51 l). Population pharmacokinetic analysis of the same data gave similar mean values for systemic clearance and half-life, 0.26 l/day and 20.4 days, respectively. The gender- related pharmacokinetic differences are not considered to be clinically relevant and dose adjustment is not required. No pharmacokinetic data are available in patients with hepatic or renal impairment.

1.2.2 Tocilizumab

Within the remit of this study Tocilizumab is being used in accordance with its UK licence. Tocilizumab (RoActemra, Roche) is a humanised monoclonal antibody that inhibits cytokine interleukin-6 (IL-6). Reducing the activity of IL-6 may reduce inflammation in the joints, prevent long-term damage, improve quality of life and function, and relieve certain systemic effects of rheumatoid arthritis. Tocilizumab binds specifically to both soluble and membrane-bound IL-6 receptors (sIL-6R and mIL-6R). Tocilizumab has been shown to inhibit sIL-6R and mIL-6R-mediated signalling. IL-6 is a pleiotropic pro-inflammatory cytokine produced by a variety of cell types including T- and B-cells, monocytes and fibroblasts. IL-6 is involved in diverse physiological processes such as T-cell activation, induction of immunoglobulin secretion, induction of hepatic acute phase protein synthesis and stimulation of haemopoiesis.

Tocilizumab in combination with methotrexate (MTX), is indicated for the treatment of moderate to severe active rheumatoid arthritis (RA) in adult patients who have either responded inadequately to, or who were intolerant to, previous therapy with one or more disease-modifying anti-rheumatic drugs (DMARDs) or tumour necrosis factor (TNF) antagonists. In these patients, Tocilizumab can be given as monotherapy in case of intolerance to MTX or where continued treatment with MTX is inappropriate. Tocilizumab has been shown to reduce the rate of progression of joint damage as measured by X ray and to improve physical function when given in combination with methotrexate.

Pharmacokinetic properties

The pharmacokinetics of Tocilizumab were determined using a population pharmacokinetic analysis on a database composed of 1793 RA patients treated with a one-hour infusion of 4 and 8 mg/kg Tocilizumab every four weeks for 24 weeks. The following parameters (predicted mean±SD) were estimated for a dose of 8 mg/kg Tocilizumab given every four weeks: steady- state area under curve (AUC)=35000±15500 h µg/ml, trough concentration (Cmin)=9.74±10.5 µg/ml and maximum concentration (Cmax)=183±85.6 µg/ml, and the accumulation ratios for AUC and Cmax were small: 1.22 and 1.06, respectively. Following intravenous administration, Tocilizumab undergoes biphasic elimination from the circulation. The linear clearance was estimated as a parameter in the population pharmacokinetic analysis and was 12.5 ml/h. The concentration-dependent non-linear clearance plays a major role at low Tocilizumab concentrations. Once the non-linear clearance pathway is saturated, at higher Tocilizumab concentrations, clearance is mainly determined by the linear clearance. The t1/2 of Tocilizumab was concentration-dependent.

At steady-state following a dose of 8 mg/kg every four weeks, the effective t1/2 decreased with decreasing concentrations within a dosing interval from 14 days to 8 days.

1.3 Clinical Data

1.3.1 Rituximab

Clinical outcomes
The efficacy and safety of Rituximab in alleviating the symptoms and signs of rheumatoid arthritis in patients with an inadequate response to TNF-inhibitiors was demonstrated in a pivotal randomized, controlled, double-blind, multicenter study (REFLEX).
REFLEX evaluated 517 patients that had experienced an inadequate response or intolerance to one or more TNF inhibitor therapies. Eligible patients had active rheumatoid arthritis, diagnosed according to the criteria of the American College of Rheumatology (ACR). Rituximab was administered as two IV infusions separated by an interval of 15 days. Patients received 2 x 1000 mg intravenous infusions of Rituximab or placebo in combination with MTX. The primary endpoint was the proportion of patients who achieved an ACR20 response at week 24. Patients were followed beyond week 24 for long term endpoints, including radiographic assessment at 56 weeks and at 104 weeks. During this time, 81% of patients, from the original placebo group received Rituximab between weeks 24 and 56, under an open label extension study protocol.

Radiographic outcomes
Structural joint damage was assessed radiographically and expressed as change in modified total Sharp Score (mTSS) and its components, the erosion score and joint space narrowing score.
In the REFLEX study, conducted in patients with inadequate response or intolerance to one or more TNF inhibitor therapies, receiving Rituximab in combination with methotrexate demonstrated significantly less radiographic progression than patients originally receiving methotrexate alone at 56 weeks. Of the patients originally receiving methotrexate alone, 81 % received Rituximab either as rescue between weeks 16-24 or in the extension trial, before week 56. A higher proportion of patients receiving the original Rituximab/MTX treatment also had no erosive progression over 56 weeks

Quality of life outcomes
Significant reductions in disability index (HAQ-DI) and fatigue (FACIT-Fatigue) scores were observed in patients treated with Rituximab compared to patients treated with methotrexate alone. The proportions of Rituximab treated patients showing a minimal clinically important difference (MCID) in HAQ-DI (defined as an individual total score decrease of >0.22) was also higher than among patients receiving methotrexate alone

1.3.2 Tocilizumab

Clinical outcomes

In a number of studies, patients treated with Tocilizumab had statistically significant higher ACR 20, 50, 70 response rates at 6 months compared to control. In The AMBITION study, superiority of Tocilizumab was demonstrated against the active comparator MTX.

The treatment effect was similar in patients independent of rheumatoid factor status, age, gender, race, number of prior treatments or disease status. Time to onset was rapid (as early as week 2) and the magnitude of response continued to improve with duration of treatment. Continued durable responses were seen for over 3 years in the ongoing open label extension of a number of clinical trials - AMBITION, LITHE, OPTION, TOWARD and RADIATE. Patients in the aforementioned studies had a mean Disease Activity Score (DAS28) of 6.5–6.8 at baseline. Significant reduction in DAS28 from baseline (mean improvement) of 3.1–3.4 were observed in Tocilizumab-treated patients compared to control patients (1.3-2.1). The proportion of patients achieving a DAS28 clinical remission (DAS28 < 2.6) was significantly higher in patients receiving Tocilizumab (28–

34%) compared to 1–12% of control patients at 24 weeks. In study II, 65% of patients achieved a DAS28 < 2.6 at week 104 compared to 48% at 52 weeks and 33% of patients at week 24.

Radiographic response

In the LITHE study, patients with an inadequate response to MTX, inhibition of structural joint damage was assessed radiographically and expressed as change in modified Sharp score and its components, the erosion score and joint space narrowing score. Inhibition of joint structural damage was shown with significantly less radiographic progression in patients receiving Tocilizumab compared to control. In the open-label extension of this study the inhibition of progression of structural joint damage in Tocilizumab plus MTX-treated patients was maintained in the second year of treatment. The mean change from baseline at week 104 in total Sharp-Genant score was significantly lower for patients randomised to Tocilizumab plus MTX ($p<0.0001$) compared with patients who were randomised to placebo plus MTX.

Quality of life outcomes

Tocilizumab-treated patients reported an improvement in all patient-reported outcomes (Health Assessment Questionnaire Disability Index - HAQ-DI), Short Form-36 and Functional Assessment of Chronic Illness Therapy questionnaires. Statistically significant improvements in HAQ-DI scores were observed in patients treated with Tocilizumab compared with patients treated with DMARDs. During the open-label period of LITHE study, the improvement in physical function has been maintained for up to 2 years.

Rationale and Risks/Benefits

This is an open labelled randomised controlled clinical trial investigating the use of synovial B cell histo-pathology as a potential diagnostic biomarker to stratify patients response to Rituximab therapy. Currently, NICE guidelines suggest the use of Rituximab in all patients following inadequate response to anti -TNF therapy. Inadequate response to Rituximab would allow for the use of Tocilizumab (IL-6 receptor monocloncal antibody). In this study patients will be randomised to receive either Rituximab or Tocilizumab. No placebo arm has been included, as withholding an approved potentially beneficial therapy would not be comparable with good standards of clinical practice. Tocilizumab has been approved by NICE for the use in patients with moderate to severe RA (NICE, http://www.nice.org.uk/CG79). Thus, there will be no greater risk from administered pharmacotherapy during this study than would be expected in routine clinical care.

All patients will have either US guided or arthroscopic synovial biopsies which would not necessarily be considered routine clinical care and thus the main risks to patients enrolled would be associated with this interventional procedure. Through the MRC-funded Pathobiology of Early Arthritis Cohort (PEAC) initiative (see below and http://www.peac-mrc.mds.qmul.ac.uk/index.php) we have developed a National Training Centre for the performance of minimally invasive ultrasound (US) guided synovial biopsies. The procedure itself has excellent safety and tolerability and can be applied to both large and small joints in most patients. Arthroscopic biopsies, whilst being technically more complicated and requiring theatre time, have been extensively validated with respect to tissue quality in therapeutic intervention studies[14]. Participating centres will use either one of the above techniques depending on experience, resources and facilities. The type of biopsy technique performed will be documented for all participants.

Our group has previously suggested that one mechanism for treatment resistance in Rituximab may be the survival of self-sustaining, B cell niches within the synovium[15]. Recent histological data has demonstrated a correlation of clinical response at 16 weeks following Rituximab and levels of synovial membrane B-cell depletion[16]. Likewise, there is evidence (though limited by the small number of patients in these studies only 8-10 patients) that synovial tissue biomarkers are associated with anti-TNF response[17,18]. No data is available with regard to IL-6 receptor blockade therapy. The need for synovial tissue analyses compared to peripheral blood is also emphasized by recent work indicating that disease biomarkers are enriched 50-100 fold in the synovial tissue compared with the blood[19]. In addition, pharmacological response signatures in the blood are not

helpful as, for example, downstream pathway toTNF are modulated in all anti-TNF treated patients, irrespective of clinical response[20]. Finally, the need for a quantitative integration between tissue biomarkers and blood biomarkers has been obvious for many years in multiple fields of medicine e.g., abnormal creatinine or liver enzymes represent important blood biomarkers of tissue pathology, but they are not informative of the respective specific renal or liver pathology. More importantly, as seen in breast cancer, biomarkers of prognosis and therapeutic response are expressed only at tissue level (e.g. ER, HER)[21].

We have strong evidence emerging from the MRC-funded Pathobiology of Early Arthritis Cohort (PEAC) initiative (220 recruited, target 300 by April 2012 - http://www.peac-mrc.mds.qmul.ac.uk/index.php) that RA patients can be classified into at least 3 histo-morphological patterns e.g. Fibroblast (pauci-immune), Lymphoid (B cell rich) and Myeloid (rich in monocytes but poor in B cells). We have also evidence that the PEAC histopathology patterns correspond to different transcriptomic signatures. More important still, we have strong pilot data in a biopsy-based study of 21 RA patients (anti-TNF-ir) that a significantly higher proportion of patients with synovial B cell-rich pattern respond to Rituximab compared with a synovial B cells-poor pattern and vice versa no-response is associated with absence/scarce B cells (chi squared $p<0.05$). Crucially, as mentioned above, synovial tissue can nowadays be obtained from most patients via either US guided or arthroscopic biopsy technique, both from large and small joints, through a minimally invasive approach, thus, potentially benefiting all patients from stratified medicines. The diagnostic tool emerging from this proposal could be adapted for execution in all NHS accredited clinical pathology Units. Thus, this study will develop a diagnostic tool (immunohistochemical analysis of synovial tissue) for patient stratification into responsive/non-responsive categories with respect to Rituximab therapy. The proposed research also has the potential to contribute work of significant clinical advantage for the treatment of rheumatoid arthritis (RA) and provide a measurable positive impact on health economics for patient benefit and the wider NHS.

2 TRIAL OBJECTIVES AND DESIGN

2.1 Trial Objectives

The main aim of this project is to test the hypothesis that the presence or absence of specific synovial cellular and molecular signatures (B cells and B cell-associated signatures), assessed following a synovial tissue biopsy, will enrich for response/non-response to the B cell depleting anti-CD20 monoclonal antibody (mAb) Rituximab. In addition, we will examine if clinical response is associated with inhibition of B cell-linked pathways within the synovium and dependent on local B cell lineage depletion and whether survival of auto-reactive B cells within “protected” synovial niches are responsible for B-cell joint re-population and disease resistance-relapse?

Therefore, the overarching hypothesis is whether a diagnostic synovial biopsy showing a B-cell “rich/poor pathotype” define specific disease responsive/resistant subsets for patient stratification and help rationalize biologic drug choice.

Therefore, while this study can be thought of as taking place in three distinct and separate synovial histomorphological phenotypes (B cell rich, B cell poor and Germinal centers);
(i) The primary aim of this project is to show that in patients failing anti-TNF therapy, with a B cell poor synovial pathotype, Tocilizumab is superior to Rituximab therapy.
(ii) For the B-cell rich synovial pathotypes, we aim to show non-inferiority of Rituxumab compared to Tocilizumab.
(iii) Germinal Centre pathotypes will constitute an exploratory component to the trial as insufficient power will be generated to show a significant difference in clinical response between each treatment. Following a sub-analysis of the pilot data we established that patients showing a germinal centre pathotype are more likely to resistant to biological therapy (3 of 4 non-responders as seen in the pilot data) thus we will take a mechanistic approach to this population of likely resistant patients and explore the predominant histological pattern and whether destruction of these structures relates to clinical response.

2.2 **Trial design**

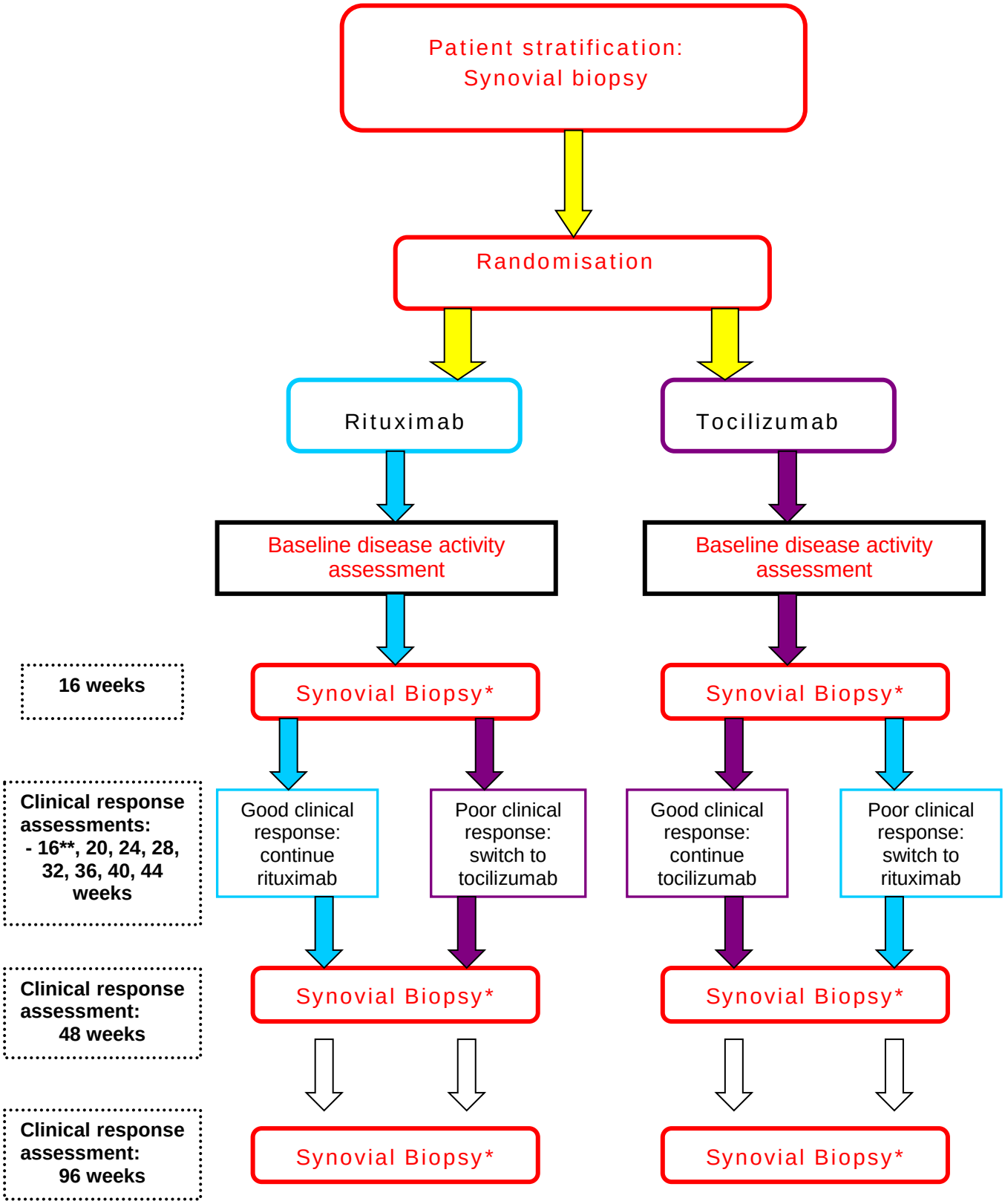
This is a multi-site, multi-country, open-label randomised controlled clinical trial. Patients recruited to this study will undergo a synovial biopsy prior to randomisation. Possible synovial biopsy sites are the knee, elbow, shoulder, wrist, ankle, MCP, PIP, and MTP joints.

Patients will subsequently be stratified in to 3 groups (B Cell Poor, B Cell Rich, Germinal Centres (GC) Rich) according to the following B-cell score prior to therapeutic intervention and by site (Lead site-QMUL or other). All participating site staff will be blinded to the pathotype (B Cell Poor, B Cell Rich, Germinal Centre). This result will be recorded centrally prior to randomisation of the patient.

Note:
In a small number of cases, patients may be randomised within a fourth 'unknown' strata if a biopsy result is not yet obtained, or the biopsy cannot be classified at the time of randomisation, however, any biopsies that are later classified will be included in analysis of the trial data.

Patients with a biopsy of unknown pre-randomisation, and where a classification cannot be obtained should remain in the study as the data collected from blood biomarkers and other trial assessments will contribute to data analysis.

2.3 Study Scheme Diagram



*Biopsy at 16, 48 and 96 weeks are optional

**A patient initially randomised to Rituximab and deemed a responder at Week 16 will be retreated if their change in CDAI from baseline is < 50% at subsequent follow up visits up to 48 weeks (a minimal interval of 24 weeks is required between treatment cycles i.e. retreatment after Week 24).

2.4 Study Population

2.4.1 Number of Subjects and Subject Selection

Number of subjects to be enrolled = at least 86 B-cell poor and at least 51-B-cell rich patients. Recruitment will stop in December 2017or once we have achieved both minima, whichever comes first. It is estimated that 160 patients are required to achieve this as further detailed in section 6.5. Patients will be recruited from within the Rheumatology department who have been referred by their consultant Rheumatologists for a second line biological agent following failure of at least 1 anti-TNF agent.

Active R4-RA trial sites may utilise Participant Identification Centres (PICs) to identify potential participants and refer them to active R4-RA trial sites for participation in the trial and conduct of all research activities relating to the trial.

2.4.2 Inclusion Criteria

Patients will be recruited with active RA:

1. Patients who have failed anti-TNF therapy (inadequate responders – ir). Note; this includes patients who have failed anti-TNF therapy because of reactions.
2. Who are eligible for Rituximab therapy according UK NICE guidelines.*
3. Patients should be receiving a stable dose Methotrexate for at least 4 weeks prior to biopsy visit.
4. 2010 ACR / EULAR Rheumatoid Arthritis classification criteria** for a diagnosis of Rheumatoid Arthritis.
5. 18 years of age or over
6. Patient must be capable of giving informed consent
7. Willingness and ability to comply with scheduled visits, treatment plans and laboratory tests and other study procedures

*Reference to NICE guidelines
1.1 Rituximab in combination with methotrexate is recommended as an option for the treatment of adults with severe active rheumatoid arthritis who have had an inadequate response to or intolerance of other disease-modifying anti-rheumatic drugs (DMARDs), including treatment with at least one tumour necrosis factor α (TNF-α) inhibitor therapy.

** The ACR/EULAR classification for a diagnosis of RA could have been at any time in the patient's disease history; the score does not need to be 6 or more at screening.

2.4.3 Exclusion Criteria

1. Women who are pregnant or breast-feeding
2. Women of child-bearing potential, or males whose partners are women of child-bearing potential, unwilling to use effective contraception during the study and for at least 12 months after stopping study treatment.
3. History of or current primary inflammatory joint disease, or primary rheumatological autoimmune disease other than RA (if secondary to RA, then the patient is still eligible)
4. Prior exposure to Rituximab or Tocilizumab for the treatment of RA
5. Treatment with any investigational agent ≤ 4 weeks prior to baseline (or < 5 half-lives of the investigational drug, whichever is the longer).
6. Intra articular or parenteral corticosteroids ≤ 4 weeks prior to biopsy visit (Visit 2).
7. Oral prednisolone more than 10mg per day or equivalent ≤ 4 weeks prior to biopsy visit (Visit 2)
8. Active infection.
9. Septic arthritis within a native joint within the last 12 months.
10. Sepsis of a prosthetic joint within 12 months or indefinitely if the joint remains in situ.
11. Known HIV or active hepatitis B/C infection. Hepatitis B screening test must be performed at or in the preceding 3 months of screening visit.
12. Latent TB infection unless they have completed adequate antibiotic prophylaxis.
13. Malignancy (other than basal cell carcinoma) within the last 10 years

14. New York Heart Association (NYHA) grade 3 or 4 congestive cardiac failure.
15. Demyelinating disease.
16. Latex allergy or allergy to any excipients of Rituximab or Tocilizumab
17. Any other contra-indication to the study medications as detailed in their summaries of product characteristics (SmPC), including low IgG levels at clinician's discretion.
18. Receipt of live vaccine <4 weeks prior to first infusion
19. Major surgery in 3 months prior to first infusion
20. Presence of a transplanted organ (with the exception of a corneal transplant >3 months prior to screening)
21. Known recent substance abuse (drug or alcohol)
22. Poor tolerability of venepuncture or lack of adequate venous access for required blood sampling during the study period.
23. Patients unable to tolerate synovial biopsy or in whom this is contraindicated including patients on anti-coagulants (oral anti-platelet agents are permitted)
24. Patients currently recruited to other clinical trial(s) involving an investigational medicinal product (except any observational follow-up periods not involving an IMP).
25. Other severe acute or chronic medical or psychiatric condition, or laboratory abnormality that would impart, in the judgment of the investigator, excess risk associated with study participation or study drug administration, or which, in the judgment of the investigator, would make the patient inappropriate for entry into this study.

The PI reserves the right to exclude patients at his centre if they have concerns regarding compliance with the study procedures or any other aspect of the study eligibility not necessarily limited to the above exclusion criteria.

2.4.4 Criteria for Premature Withdrawal

A subject may withdraw from the study at any time at his/her own request, or may be withdrawn from trial treatment at any time at the discretion of the investigator for safety, behavioral or administrative reasons. Please see section 4.14.

3 INVESTIGATIONAL MEDICINAL PRODUCT

3.1 List and definition of each IMPs

Rituximab
Rituximab is a genetically engineered chimeric mouse/human monoclonal antibody representing a glycosylated immunoglobulin with human IgG1 constant regions and murine light-chain and heavy-chain variable region sequences.

Tocilizumab
Tocilizumab humanised IgG1 monoclonal antibody against the human interleukin-6 (IL-6) receptor produced in Chinese hamster ovary (CHO) cells by recombinant DNA technology

3.2 Formulation of IMP

Rituximab
Rituximab is available as 50ml single-use vials containing 500mg Rituximab for infusion (10mg/ml)
Rituximab is a clear, colourless liquid

Tocilizumab
Tocilizumab is available in 20mg/ml vials in a concentrate for intravenous infusion. The vials are available in 4ml (80mg), 10ml (200mg), and 20ml (400mg).

3.3 IMP Supply

Rituximab

Rituximab will be prescribed according as per license and thus will be sourced from local clinical supplies at each trial site. The IMP will be labelled as clinical trial material.

Tocilizumab

Tocilizumab will be prescribed according as per license and thus will be sourced from local clinical supplies at each trial site. The IMP will be labelled as clinical trial material.

3.4 Prescription of IMP

Rituximab

Rituximab will be prescribed by a physician as a member of the study team, using trial specific prescription forms. Prescription forms should be stored in the trial Pharmacy File and must be available for review for the purposes of monitoring visits/audit inspections throughout the study duration.

Tocilizumab

Tocilizumab will be prescribed by a physician as a member of the study team, using trial specific prescription forms. Prescription forms should be stored in the trial Pharmacy File and must be available for review for the purposes of monitoring visits/audit inspections throughout the study duration.

3.5 Preparation and Administration of IMP

3.5.1 Rituximab

Preparation and administration (including pre-medication administration) will be performed by a suitably trained member of the local study team as per local policy and the SmPC, therefore instructions detailed below may be subject to some local variation.

Instructions for Dilution and Suitable Diluent:

Aseptically withdraw 1000mg (100ml) of Rituximab.
Slowly add the total volume of Rituximab (100mls) to a 500ml bag of sodium chloride 0.9%. To mix, gently invert the bag in order to avoid foaming. Do not shake. Final concentration will be 1.67mg/ml.

If, according to local policy, a different dilution is used (i.e. different volume of sodium chloride 0.9% solution for injection or 5% D-Glucose in water**), the final concentration of the drug should in any case be between 1-4mg/ml**
Care must be taken to ensure the sterility of the prepared solution – aseptic technique must be observed.
Inspect the bag visually for any particulate matter and discolouration prior to administration – discard the solution if observed.
The prepared infusion should be used immediately.

Method and Rate of Administration:

Pre-medication should be prescribed and administered 30 minutes prior to the start of infusion:

Drug	**Dose**	**Route**	**Frequency**
Methylprednisolone	100mg	IVI	Stat
Chlorphenamine	10mg	IVB	Stat
Paracetamol	1000mg	PO	Stat

Observations e.g. temperature, blood pressure, pulse and respiratory rate should also be carried out prior to the start of infusion.

Example using IV Volumat Pump

The Rituximab entry in the pump library defaults to 1000mg in 600ml (as described above) and defaults to an initial rate of 50mg/hr (30mls/hour).

First infusion of each course
The following infusion rates are based on a final concentration of 1.67mg/ml of rituximab. In case a different dilution is used according to local policy, the following rates in mg/hour must be respected (the rates in ml/hour will differ).

IV infusion: Initial rate: 50 mg/hr (30mls/hour); increase rate by 50 mg/hr (30mls/hour) every 30 minutes if tolerated, to a maximum of 400 mg/hr (240mls/hour).

	Rate – mg/hour	**Rate – mls/hour**
Initial rate	50mg/hour	30mls/hour
After 30mins (if tolerated)	100mg/hour	60mls/hour
After 30mins (if tolerated)	150mg/hour	90mls/hour
After 30mins (if tolerated)	200mg/hour	120mls/hour
After 30mins (if tolerated)	250mg/hour	150mls/hour
After 30mins (if tolerated)	300mg/hour	180mls/hour
After 30mins (if tolerated)	350mg/hour	210mls/hour
After 30mins (if tolerated)	400mg/hour	240mls/hour

Second infusion of each course
As per the Rituximab SmPC, subsequent doses can be infused at an initial rate of 100 mg/hr, and increased by 100 mg/hr increments at 30 minute intervals, to a maximum of 400 mg/hr.

Alternative subsequent, faster, infusion schedule for second and subsequent infusion as per the Rituximab SmPC:

If patients did not experience a serious infusion related reaction with their first or subsequent infusions of a dose of 1000 mg MabThera administered over the standard infusion schedule, a more rapid infusion can be administered for second and subsequent infusions using the same concentration as in previous infusions (4 mg/mL in a 250 mL volume or equivalent). Initiate at a rate of 250mg/hour for the first 30 minutes and then 600 mg/hour for the next 90 minutes. If the more rapid infusion is tolerated, this infusion schedule can be used when administering subsequent infusions.
Patients who have clinically significant cardiovascular disease, including arrhythmias, or previous serious infusion reactions to any prior biologic therapy or to rituximab, should not be administered the more rapid infusion.

3.5.2 Tocilizumab

Preparation and administration will be performed by a suitably trained member of the local study team as per local policy and the SmPC, therefore instructions detailed below may be subject to some local variation.

Instructions for Dilution and Suitable Diluent:

- The volume of Tocilizumab concentrate required for the patients dose should be calculated.
- Using aseptic technique the required volume of sodium chloride 0.9% should be removed from a 100ml infusion bag.
- The required volume of Tocilizumab should be withdrawn from the vial and placed in the 100ml infusion bag to give a final volume of 100ml

- To mix the solution, gently invert the infusion bag to avoid foaming. Do not shake.

Method and Rate of Administration:
IV infusion:
The final 100ml infusion bag should be administered by IV infusion over a one hour period[1].

Example Using IV Volumat Pump:
The pump does not have a preset setting for Tocilizumab.

Example Using Injectomat Syringe driver:
The syringe driver does not have a preset setting for Tocilizumab.

Example Calculation: (Adult Patients)
For a 70kg, the dose is usually 560mg every 4 weeks (70kg x 8mg/kg). This dose requires 28ml of Tocilizumab concentrate – ie 20ml from a 1 x 400mg vial and 2 x 4ml (2 x 80mg) doses. Twenty eight ml is withdrawn from the 100ml infusion bag and the 28ml form the vials added to the infusion bag. The resulting solution is then given as an IV infusion over a one hour period.

Flushes Compatible:
Sodium Chloride 0.9%

Special Handling Precautions:
The reconstituted solution should be used immediately due to sterile concentrate not containing any preservatives.

The Tocilizumab will be administered at room temperature by controlled infusion into an arm vein over a one hour period. In exceptional cases this time may be extended to up to 6 hours. The infusion speed must be 10 mL/hour for 15 minutes and then increased to 130 mL/h to complete the dosing over 1 hour. The entire 100 mL content of the infusion bag must be administered. 20 mL of normal saline will be administered following the infusion of study medication to flush the remaining study medication through the intravenous set.

3.6 Accountability/Receipt/Storage and Handling of IMP

The local Principal Investigator is responsible for the control of drugs under investigation at their site. Adequate records (e.g. Drug Dispensing Log) of the study drug will be maintained. Accountability will be assessed by maintaining adequate drug dispensing and return records. This will be delegated to the local site pharmacy. The IMP will be stored by the local pharmacy. Accurate records will be kept for each study drug provided.

Dispensing of IMP
A Drug Dispensing Log will be kept current and will contain the following information:
• the identification of the patient to whom the study medication was dispensed
• the date[s], quantity of the study medication dispensed to the patient
• the date[s] and quantity of any unused study medication
All records and drug supplies must be available for the purpose of monitoring visits/audit inspections

Rituximab and Tocilizumab may be reconstituted under conditions approved by the local hospital pharmacy.

Used or partially used vials should be disposed of under conditions approved by the local hospital pharmacy.

Unused vials may be returned to pharmacy if approved by the local hospital pharmacy.

3.7 IMP Stability

Rituximab
Riituximab solutions for infusion will be stored at a controlled temperature 2 -8^{o}C (36-46^{o}F) for 24 hours. Rituximab solutions for infusion have been shown to be stable for an additional 24 hours at room temperature. However, since Rituximab solutions do not contain a preservative, diluted solutions should be stored refrigerated (2-8^{o}C). A temperature log will be kept on which the storage temperature of Rituximab solutions is recorded at least once a day. No incompatibilities between Rituximab and polyvinylchloride or polyethylene bags have been observed. Any deviations from the necessary temperature range will be documented and appropriate action taken.

Tocilizumab
All Tocilizumab vials must be stored at a controlled temperature of 2-8°C. The infusion bag of Tocilizumab in saline may be made up within 24 hours of dosing and must be stored in a refrigerator at 2-8°C, provided the site takes precautions to prepare the infusion aseptically. A temperature log must be kept, on which the storage temperature of the Tocilizumab and infusion bags is recorded at least once a day. Any deviations from the necessary temperature range will be documented and appropriate action taken.

3.8 Prior and Concomitant Anti-Rheumatic Therapies

3.8.1 Anti-TNF
Patients Enrolled into this study will have received anti-TNF therapy in accordance with NICE guidelines. Previous anti-TNF agents will be recorded. There must be a minimum washout period of 4 weeks for Infliximab and a 2 weeks for all other anti-TNFs prior to the biopsy visit.

3.8.2 DMARDs
Patients must have received and continue to receive Disease Modifying Anti-Rheumatic Drugs (DMARDs). Patients must be stable on Methotrexate (and other DMARDs as applicable) for at least 4 weeks prior to the biopsy visit.

3.8.3 NSAIDs
Patients will be permitted to be on NSAIDs at any time throughout the duration of the study.

3.8.4 Corticosteroids
Patients may receive corticosteroid therapy throughout the trial, at the discretion of the treating clinician. However, the corticosteroid dose should be stable and **not exceed** prednisolone 10mg/day (or equivalent) during the time-points listed below.
Intra-articular and parenteral corticosteroids may also be used throughout the trial, but **not** during the time-points listed below.

Within 4 weeks prior to:

- Visit 2 (Biopsy)
- Visit 3 (Baseline)
- Visit 7 (16 weeks; regardless of optional biopsy being taken)
- The subsequent 16 week assessment following second drug initiation for patients who switch treatment after failure of their first therapy
- Any subsequent optional biopsy visits – biopsy visit prior to 48 weeks or Visit 15 (48 weeks), and Visit 17 (96 weeks).

Note: Any injected joints should be excluded from the joint count assessment for 12 weeks following the injection.

3.8.5 Other Medications

Other medications are permitted as required during the study and should be recorded on the applicable Visit Case Report Form (CRF).

3.9 Dose modification/reduction/ delay

Adherence to the planned dose regimen of study medication is required unless an adjustment is necessary for safety events as per applicable SmPCs
Note: For patients receiving Tocilizumab 8 mg/kg during the period of this study, the dose may be lowered to 4 mg/kg to manage safety events. See section 4.13.

4 STUDY PROCEDURES

4.1 Informed Consent Procedures

Written informed consent will be obtained from each patient by the Principal Investigator or designee. Informed consent will be prepared according to NRES and study sponsor requirements for informed consents.

Patients who are candidates for the study will receive a Patient Information Sheet (PIS) which explains the purpose of the trial and highlights the benefits and risks of participation in the trial. Patients must be given adequate time (minimum 24 hours) to review the information and must have the opportunity to ask the Principal Investigator or designee any questions relating to the trial. Following this, the patient must sign an informed Consent Form (CF) in the presence of the Principal Investigator or designee who must then countersign the CF.

Written consent must be obtained prior to any study-specific procedures being performed, including any study specific screening procedures prior to randomisation. At the time of consent, participants must be informed that they have the right to withdraw their participation in the trial at any stage and that doing so will not prejudice their future clinical management and care.
The written consent will be taken by a clinician, who has signed / dated the staff authorisation / delegation log. The process of obtaining written consent will be clearly documented in the patient's medical notes.

4.2 Screening (Visit number 1)

.
Patients may be screened up to 6 weeks prior to Baseline Visit. As per the study visit schedule screening will entail evaluation of:

- Inclusion and exclusion criteria
- Demographic data including age, gender
- 2010 ACR/EULAR RA classification criteria
- Systemic disease assessment (RA involvement)
- Medical history
- Procedures history
- Concomitant medication
- Anti-TNF therapy
- DMARD therapy
- Corticosteroid therapy
- Clinical examination
- Rheumatoid Factor and Anti-CCP antibodies (RF, CCP)[a]
- Routine blood tests (FBC, UE, LFT, ESR, CRP)[b]
- Total cholesterol, HDL, LDL, and triglycerides
- Immunoglobulins/Immunodeficiency panel[c]
- Hepatitis serology, HIV and IGRA[d]

- Vital signs
- Chest X-ray[e]
- ECG
- Pregnancy test
- Joint assessment
- DAS 28 assessment
- Clinical Disease Activity Index (CDAI)
- VAS Pain score

Notes:

[a] RF/CCP tests should be performed unless these tests have been done previously and do not need repeating as per local guidelines.

[b] Routine blood tests do not need to be taken if the patient has already had routine blood tests performed within 10 days of the screening visit.

[c] Immunoglobulin tests must be performed at screening unless previously performed within the last 8 weeks (to confirm trial eligibility). Maximum time between testing and infusion is 12 weeks. Immunodeficiency panels are not mandatory and to be performed as per local guidance.

[d] Hepatitis B screening must be performed unless it has been done in the preceding 3 months of the screening visit.
TB (IGRA), Hepatitis C, and HIV screening are not mandatory however risk assessment must be carried out and documented. All centres are expected to act according to local guidelines, but screening does not need to be repeated if it has been performed in the preceding 3 months of the screening visit.

[e] A chest x-ray must be performed as per routine screening for tuberculosis prior to biological therapy (depending on local guidelines). If a chest x-ray is required as per local guidelines this must be done at the screening visit to confirm the patient's eligibility, unless a chest x-ray has been done in the preceding 3 months of the screening visit and the patient must not have had any pulmonary symptoms since then.

4.3 **Biopsy visit (Visit number 2)**

Patients will receive a synovial biopsy between 1 to 3 weeks prior to their baseline visit. Patients will have the following assessments recorded prior to the synovial biopsy at this visit:

- Concomitant medication
- DMARD therapy
- Corticosteroid therapy
- Routine clinical bloods
- Study specific bloods
- Vital signs
- A pregnancy test will be performed in female patients of child bearing age
- Joint assessment
- DAS 28
- CDAI
- VAS Pain Score
- Physical function using the Health Assessment Questionnaire (HAQ)
- Pre Biopsy Assessment Form
- A Ultrasound examination of the patients joints will be performed prior to the synovial biopsy
- Synovial biopsy. Please refer to Ultrasound guided biopsy manual (particularly the decision algorithm). *

Notes:

- A synovial biopsy prior to randomisation is mandatory as part of the patient stratification process however subsequent synovial biopsies will remain optional. Patients not receiving a subsequent biopsy at 16 weeks, 48 weeks or 96 weeks will continue within the study as per protocol.
- Routine bloods do not need to be taken if the patient has already routine bloods performed within 10 days of the biopsy visit.
- The initial biopsy visit may be combined with completion of the study screening visit if all screening procedures are available and the patient is eligible for enrolment into the study. If the completion of the screening and biopsy visit occur on the same day, there is no need to repeat the procedures for vital signs, Pregnancy test, Joint Assessment, DAS28, CDAI, VAS pain score. This data will not need to be duplicated at the biopsy visit.

Randomisation into the study can only occur once the biopsy has been taken and biopsy result confirmed (B cell poor, B cell rich, GC or unknown). The randomisation procedure can occur at the baseline visit (see 4.5), or prior, to allow pharmacy time to prepare the allocated treatment.

4.4 **Randomization Procedures**

Randomisation will take place when all the screening procedures are complete and the patient is eligible for enrolment in the study. The pathotype will be recorded on the R4-RA trial database at the R4-RA Trials office. Patients will be stratified (3 strata based on B cells, or a fourth strata where result is unknown) and by site (by lead site-QMUL or other) and randomised within blocks (1:1), with random block size of 6 and 4. The local principal investigator/research nurse will log-in to secure web-based R4-RA trial database and complete Screening and Biopsy visit Case Report Forms prior to randomisation. The R4-RA Trial Office will confirm eligibility and perform the randomisation. Subsequently the assigned treatment and unique randomisation number (study number) will be allocated automatically by the application. This ensures that neither the patient nor the clinician can choose whether or not to enter the trial depending on the next allocation. The randomisation list will be prepared by the Barts CTU Statistician and securely embedded with the application code in the R4-RA trial database so that it is not accessible to end users or anyone other than the Database Programmer and a limited number of information support staff who have access to all systems. Once a participant has been allocated a treatment, there is an audit trail that prevents anyone from changing the allocation or pretending that no allocation had been made.

4.5 **Baseline visit (Visit number 3)**

All Baseline visit assessments should be performed prior to commencement of infusion of therapy.

Patients should remain blinded to their randomised treatment prior to undergoing the Baseline assessments and will be informed as soon as assessments are completed.

Patients at baseline will have the following assessments:
Concomitant Medication
DMARD therapy
Corticosteroid therapy
Clinical examination
Cardiovascular risk assessment
Routine bloods*
Vital signs
Pregnancy test in women of child bearing age.
Joint assessment
Disease activity core data set (DAS28)
Clinical Disease Activity Index (CDAI)
VAS Pain score
Physical function using the Health Assessment Questionnaire (HAQ)
SF-36
FACIT – Fatigue Questionnaire

Post Biopsy Assessment Form
Adverse events
Plain X-rays of hands and feet**

Patients will receive either Tocilizumab or Rituximab at their baseline visit depending upon randomisation.

Notes:

All baseline assessments should be done within a +/- 7 day window. *Patients randomised to receive Tocilizumab – routine blood tests should be carried out and checked prior to each infusion.
**Plain X-rays of hands and feet do not need to be taken if the patient has already had them done within 8 weeks of the Baseline visit.

4.6 **Follow up visits**

Patients will be monitored on a 4-weekly basis as shown in the study visit schedule (Section 4.9).

The CDAI, a validated composited end point, will be used to assess response to therapy as the primary outcome measure. The Health Assessment Questionnaire and SF-36 will be used to gauge functional ability and improvement in other aspects of the patients life e.g. vitality, emotional role functioning, social role functioning and mental health.

Visits 3a and 9a are specific to Rituximab patients only must attend at these time points to receive the second Rituximab infusion. Extra study specific bloods will be taken from these patients as detailed in section 4.11.4.1.

Visits 4 – 15 will be carried out 4 weekly (+/- 7 days). Visits 16 and 17 will be completed if these visits fall within the data collection period of the trial (see section 4.12). This will be for patients recruited in the earlier stages of recruitment and who have reached 72 and 96 week timepoints as applicable. Sites will be notified when the end of the period is finalised. Visit 16 will be carried out at 72 weeks from baseline (+/-14 days) and Visit 17 at 96 weeks (+/-14 days) from baseline. The Principal Investigator will need to review any non-compliance with a view to withdrawing patients at their discretion if drug schedule is adversely affected.

Patients who will not reach visit 16 (72 weeks) or visit 17 (96 weeks) timepoints may be called by telephone or attend a clinic visit to complete a post-treatment Safety Follow-up visit a minimum of 30 days after the end of the treatment period at Visit 15 (48 weeks). This will check for any adverse events during the follow up period. Details collected as part of this visit should be reported in the patient's medical notes and then added to the Safety Follow-up electronic Case Report Form (eCRF). All Adverse Events will be reported in the eCRF.

Patients who consent to optional biopsy procedure at Visit 7 (Week 16) will be asked to complete the Pre Biopsy Assessment Form at Visit 7 (week 16) and the Post Biopsy Assessment Form at Visit 8 (Week 20).

All joint assessments will be performed by a member of the local trial team who will be blinded to treatment allocation of all participants. The joint assessor should also complete the VAS physician assessment component of the VAS Pain Score questionnaire.

The principal investigator (or other delegated person(s) in the local trial team) must not perform the joint assessments, and instead will be responsible for collecting, recording and reporting data on adverse events and drug therapy at each study visit.

Delegation of these responsibilities to ensure the blind is maintained will be documented on the site signature/delegation log.

Data will be entered in the electronic CRF by the Investigator or designee who will also co-ordinate data validation checks and query resolution.

4.7 **Unscheduled Visits**

While patients will be encouraged to attend for the normal visit schedule, unscheduled visits will be undertaken if the patient is unwell or there are any concerns as to the patient's progress. If necessary, the patient may be withdrawn from the trial and the Treatment Cessation CRF must be completed (see section 4.15).

4.8 **Schedule of Treatment for each visit**

Patients randomised to Tocilizumab will have 4 weekly infusions (+/- 7 days) at each of the study visits alongside their routine assessments.

Patients randomised to Rituximab will have infusion cycles of a minimum of every 24 weeks (+/- 7 days) consisting of two infusions given 2 weeks apart (Day 0 and Day 15), but will continue to have 4 weekly visits for assessments as per the study visit schedule. A patient initially randomised to Rituximab, deemed a responder at 16 weeks (CDAI ≥50% improvement from baseline assessment) who continues to have active disease (CDAI ≥10.1) or flares (CDAI ≥10.1) will be re-treated. Patient deemed a non-responder following second cycle of Rituximab may prompt a switch in medication if prior to 48 weeks.

The treatment schedule is subject to change if patients switch treatment. Patients who are switching treatment may attend a separate visit for the administration of the new biologic agent within the +/- 7 day window as already described or can switch treatment at the following visit. (See also section 4.11.1.1 for timings for treatment switch).

4.9 **Study visit schedule**

Visit Number	1	2	3	3a [c]	4	5	6	7	8	9	9a [c]	10	11	12	13	14	15	(15b)[n]	16 [m]	17 [m]	Treatment Cessation/Early Withdrawal F/U
Timeline (weeks)	- 6 – 1 week	- 3 -1 weeks	0	2	4	8	12	16	20	24	26	28	32	36	40	44	48	(52)	72	96	-
Visit Type	Screening	Biopsy	Baseline	F/U	F/U	F/U	F/U	F/U	F/U	F/U	F/U	F/U	F/U	F/U	F/U	F/U	F/U	F/U	F/U	F/U	F/U
Informed consent	x							x									x			x	
Inclusion/Exclusion criteria	x																				
Demographics	x																				
RA classification criteria	x																				
Systemic disease assessment	x																				
Medical history	x																				
Procedures History	x																				
Allergies	x																				
Concomitant medication	x	x	x		x	x	x	x	x	x		x	x	x	x	x	x		x	x	x
Previous Anti-TNF therapy	x																				
DMARD therapy	x	x	x		x	x	x	x	x	x		x	x	x	x	x	x		x	x	x
Corticosteroid therapy	x	x	x		x	x	x	x	x	x		x	x	x	x	x	x		x	x	x
Clinical Examination	x		x		x	x	x	x	x	x		x	x	x	x	x	x		x	x	x
Cardiovascular risk assessment			x																		
RF/CCP[a]	x																				
Routine blood tests (CRP, ESR, Hb, WBC, platelets, lymphocytes, neutrophils, ALT/AST)[b]	x[b]	x[b]	x[b]		x	x	x	x	x	x		x	x	x	x	x	x		x	x	x
Total cholesterol, HDL, LDL and triglycerides	x					x								x						x	
Study specific blood tests [c]		x		x	x	x		x		x	x	x		x			x			x	
Immunoglobulins/Immunodeficiency panel [d]	x								x[d]												
Hepatitis serology, HIV, IGRA[e]	x																				
Vital signs	x	x	x		x	x	x	x	x	x		x	x	x	x	x	x		x	x	x
Chest X-ray [f]	x																				
ECG	x																				
Pregnancy test [g]	x	x	x		x	x	x	x	x	x		x	x	x	x	x	x		x	x	x

Joint assessment [h]	x	x	x		x	x	x	x	x	x		x	x	x	x	x	x		x	x	x
DAS28	x	x	x		x	x	x	x	x	x		x	x	x	x	x	x		x	x	x
CDAI	x	x	x		x	x	x	x	x	x		x	x	x	x	x	x		x	x	x
VAS Pain score [h]	x	x	x		x	x	x	x	x	x		x	x	x	x	x	x		x	x	x
HAQ score		x	x				x			x				x			x		x	x	x
SF-36 Health Survey			x				x			x				x			x		x	x	x
FACIT-Fatigue Questionnaire			x				x			x				x			x		x	x	x
Pre Biopsy Assessment Form		x						x													
Post Biopsy Assessment Form			x						x												
Adverse events		x	x		x	x	x	x	x	x		x	x	x	x	x	x	x	x	x	x
Synovial biopsy [i]		x						x									x			x	
X-ray hands and feet			x [j]							x							x			x	
US assessment [k]		x	x		x		x	x		x				x			x		x	x	
Randomisation [l]		x																			
Rituximab dispensed[P]			x	x						x[o]	X[o]										
Tocilizumab dispensed[P]			x		x	x	x	x	x	x		x	x	x	x	x					

a - RF/CCP tests should be performed unless these tests have been done previously and do not need repeating as per local guidelines.

b - At screening visit – routine blood tests do not need to be taken if the patient has already had routine blood tests performed within 10 days of the screening visit.

- At biopsy visit – routine bloods do not need to be taken if the patient has already routine bloods performed within 10 days of the biopsy visit.

c - Extra study specific bloods are required for patients randomized to receive Rituximab therapy as these patients are already attending for their second infusion of Rituximab.

d - Serum immunoglobulins must be performed at screening unless previously performed within the last 8 weeks (to confirm trial eligibility). Maximum time between testing and infusion is 12 weeks. Retests to be considered if clinically required and documented in medical notes. Serum immunoglobulins then only required subsequently for patients receiving Rituximab. These should be repeated prior to every cycle of Rituximab. Maximum time between testing and infusion is 12 weeks. This includes patients switching from Tocilizumab to Rituximab. Immunodeficiency panel is not mandatory but should be carried out as per local guidance.

e - Hepatitis B screening must be performed unless it has been done in the preceding 3 months of the screening visit. TB (IGRA), Hepatitis C, and HIV screening are not mandatory however risk assessment must be carried out and documented. All centres are expected to act according to local guidelines.

f - A chest x-ray must be performed as per routine screening for tuberculosis prior to biological therapy (depending on local guidelines). If a chest x-ray is required as per local guidelines this must be done at the screening visit to confirm the patient's eligibility, unless a chest x-ray has been done in the preceding 3 months of the screening visit and the patient must not have had any pulmonary symptoms since then.

g - A pregnancy test will be performed at each study visit for female patients of child bearing age irrespective of the use of contraceptive methods.

h - Joint assessments and VAS physician assessment to be completed by the nominated 'blinded joint assessor'.

i - A baseline synovial biopsy is mandatory as part of the patient stratification process however subsequent synovial biopsies will remain optional. Patients not receiving a subsequent biopsy will continue within the study as per protocol. Biopsy taken at Biopsy visit (mandatory), 16 weeks (optional), at a subsequent visit when a patient switches treatment as per protocol OR otherwise at week 48 (optional), 96 weeks (optional).

- The initial biopsy visit may be combined with completion of the study screening visit if all screening procedures are available and the patient is eligible for enrolment into the study. If the completion of the screening and biopsy visit occur on the same day, there is no need to repeat the procedures for vital signs, Pregnancy test, DAS28, CDAI, VAS pain score. This data will not need to be duplicated at the biopsy visit.

j - Plain X-rays of hands and feet do not need to be taken if the patient has already had them done within 8 weeks of the Baseline visit.

k - US assessments may be optional at some participating sites.

l - Randomization can occur as soon as the biopsy result is obtained and prior to the scheduled baseline visit to allow sufficient preparation time for pharmacy.

m - Visits 16 and 17 will be completed if these visits fall within the data collection period of the trial. This will be for patients recruited in the earlier stages of recruitment. Sites will be notified of the end of the data collection period (this will be confirmed when recruitment is completed).

n - This is only for patients who will not reach visit 16 (72 weeks) or visit 17 (96 weeks) timepoints The post-treatment visit/call should be scheduled at least 30 days after the last treatment (48 weeks) in order to identify any adverse events. If a scheduled follow-up visit as part of clinical care falls within this time frame AEs can be assessed as part of this visit, with no requirement for an additional visit/call.

o	-Patients on rituximab may be re-treated after 24 weeks (24 weeks is the minimum amount of time for re-treatment)
p	Treatment schedules are subject to change if the patient switches treatment.

Notes:

- Patients who are switching treatment may attend for a second time within the +/- 7 day visit window for the infusion (Visits 7 – 14).
- The last trial prescription will be at visit 14. The decision of the patient's ongoing treatment will be made by the treating clinician
- Patients randomised to receive Tocilizumab – routine blood tests should be carried out and checked prior to each infusion.
- Study specific bloods – visit schedule changes:
  i) If a patient receives a cycle of rituximab therapy within the first 48 weeks of the study and it is not in line with the visit schedule detailed above i.e. the patient is not retreated at 24 weeks, then the study blood schedule will **shift** with the re-treatment schedule (e.g. if patient remained in remission until week 28 and then flared and was retreated at week 32 then study visit bloods should be taken prior to the 1st infusion (week 32) and 2nd infusion (week 34), and then at week 36 and week 44 study visits.
  ii) Similarly, patients who switch treatment from Tocilizumab to Rituximab will commence an amended study specific blood schedule e.g. if a patient switches from Tocilizumab to Rituximab at week 16, study specific bloods will be required prior to the 1st infusion (week 16) and 2nd infusion (week 18), then at week 20 and week 28 study visits.
  iii) All patients will have study specific bloods at week 48 and week 96 visits (if these fall within the data collection period of the trial)..

4.10 **Completion of Trial Treatment**

The duration of trial treatment is 48 weeks. The follow-up period is between 48 weeks and 96 weeks if these visits fall within the data collection period of the trial (see section 4.12). This will be for patients recruited in the earlier stages of recruitment and who have reached 72 and 96 week timepoints as applicable.

Patients that complete trial treatment, and those that withdraw prematurely, will require ongoing treatment for their condition. The decision for ongoing treatment will be made by the treating clinician, following assessment of response to previous treatments, as per local guidelines. The ongoing treatment plan will be discussed fully with the patient.

Patients that are randomized to Tocilizumab and who are responding to this treatment must be informed that they may not be able to continue on this treatment after completion of the trial (applicable as per NICE guidelines in the UK).and other national guidelines in non-UK sites.

4.11 **Study Outcome Measures**

4.11.1 Clinical outcomes

Patients will be assessed for disease activity using the CDAI (Clinical disease activity index), DAS 28 (CRP/ESR), Health Assessment Questionnaire (HAQ), Short Form 36 and FACIT Fatigue questionnaire as described below.

4.11.1.1 CDAI

The components of the CDAI (Clinical disease activity Index) are tender joints (28 joint count), the number of swollen joints (28 joint count), a Patient global health index (10 cm VAS) and physician global health index (10 cm VAS). This provides an assessment of Rheumatoid disease activity on a scale from 0-76.

CDAI scores

High disease activity:	>22
Moderate disease activity:	10.1 – 22
Low disease activity	2.8 – 10
Remission	< 2.8

Non-responders – CDAI improvement of less than 50% from baseline.
Patients may be deemed non-responders at the discretion of the treating physician if they have achieved a CDAI response of ≥ 50% from baseline but have not reached low disease activity (CDAI of 10 or less)
Responders – CDAI improvement of more than 50% from baseline.

- Small response – CDAI ≥ 50% improvement from baseline assessment
- Moderate response – CDAI ≥ 75% improvement form baseline
- Good response – CDAI ≥ 85% improvement form baseline

Treatment response will be assessed at 16 weeks and at all subsequent 4 weekly assessments up to 48 weeks:

- Patients deemed as responders at 16 weeks will continue on their allocated treatment.

Patients deemed treatment failures at 16 weeks, will be switched to the other therapeutic option.

- Patients on Tocilizumab showing initial clinical response by 16 weeks may be classified as a secondary failure at subsequent study visits (up to 48 weeks), at the physician's discretion, if their change in CDAI from baseline is < 50% at any subsequent follow up visit. This will also prompt a switch to the other therapeutic option. Patients on Rituximab, who

are deemed as responders at Week 16 but their change in CDAI from baseline is < 50% at subsequent follow up visits (up to 48 weeks), will be re-treated with Rituximab. Patients on Rituximab may not be retreated before week 24 (as described in section 4.8). At any follow-up visit following Rituximab re-treatment, patients may be deemed a secondary failure at their physician's discretion if their change in CDAI from baseline is < 50% or they have ongoing disease activity (CDAI >10.1). This will prompt a switch to the other therapeutic option.

- Note: patients deemed treatment failure at week 16 can switch treatment at the week 16 visit (+/- 7 days) or at the following visit. Patients deemed as a secondary treatment failure at subsequent study visits may switch treatment either at that visit (+/- 7 days) or the following visit.

- Failure of a second biological therapy at any subsequent visit, would permit the patient to receive treatment option of the physician's discretion.

With regards to primary endpoint analysis, patients classified as a failure to second biologic will continue in the trial but the data collected (and any further treatment changes) will form an observational component of the trial.

4.11.1.2 Disease Activity Score – DAS28

The components of the DAS28 are the number of tender joints (28 joint count), the number of swollen joints (28 joint count), a Global Health index (100 mm VAS), and the CRP (in mg/L) or ESR (in mm/h). The formula for determining the DAS28 is as follows:

$$DAS28(CRP) = 0.56*\sqrt{(TJC28)} + 0.28*\sqrt{(SJC28)} + 0.36*\ln(CRP+1) + 0.014*GH\ (VAS) + 0.96$$

$$DAS28(ESR) = 0.56*\sqrt{(TJC28)} + 0.28*\sqrt{(SJC28)} + 0.70*\ln(ESR) + 0.014*GH\ (VAS)$$

The following 28 joints will be assessed for tenderness in response to pressure or passive motion: Finger Proximal Interphalangeal Joints (8), thumb Interphalangeal joint (2), metacarpophalangeal (MCP) (10), wrists (2) (includes carpometacarpal, intercarpal, and radiocarpal), elbows (2), shoulders (2), and knees (2).

DAS 28 Response criteria (for the purpose of secondary endpoints evaluation)

DAS28 improvement from baseline	Post-treatment DAS28	Category of response
< 1.2	Any	Non-responder.
> 1.2	> 5.1	Patient may be designated a non-responder at the discretion of the rheumatologist
> 1.2	> 3.2 but < 5.1	Partial responder.
> 1.2	< 3.2 but > 2.6	Good responder.
> 1.2	< 2.6	Remission

Table 1: Summary of response criteria using validated composite outcome measure DAS 28

4.11.1.3 Joint Assessment for CDAI and DAS scores

The blinded joint assessor will be blinded to trial treatment. Where possible the same joint assessor should conduct all joint assessments, in particular the baseline and Visit 7 (16 weeks) visits for primary endpoint data.

Examination of the upper extremities will be performed with the patient in the sitting position. Examination of the lower extremities will be performed with the patient supine. During the assessment of pain on passive motion, no concurrent pressure will be applied to the joint margin. During pain on passive motion testing, the joint will be moved through the full available range in order to detect any end range pain. Joint pain with palpation or pain on passive motion (either is sufficient) will be scored according to the following scale:

- No pain
- Patient states that there is pain

Assessment of Swelling: 28 joints will be assessed for the presence of swelling. The joints to be evaluated include those evaluated for tenderness. Joint swelling on palpation will be scored according to the following scale:

- No swelling
- Swelling

4.11.1.4 Health Assessment Questionnaire (HAQ)

The HAQ is usually self-administered, but may also be given face-to-face in this clinical study. The Disability Index consists of eight categories assessed by the Disability Index are 1) dressing and grooming, 2) arising, 3) eating, 4) walking, 5) hygiene, 6) reach, 7) grip, and 8) common daily activities. For each of these categories, patients report the amount of difficulty they have in performing two or three specific activities. Patients usually find the HAQ Disability Index entirely self-explanatory.

4.11.1.5 The Short Form (36) Health Survey – SF-36

The Short Form (36) Health Survey is a survey of patient health. The SF-36 is a measure of health status and is commonly used in health economics as a variable in the quality-adjusted life year calculation to determine the cost-effectiveness of a health treatment. The SF-36 consists of eight scaled scores, which are the weighted sums of the questions in their section. Each scale is directly transformed into a 0-100 scale on the assumption that each question carries equal weight.

The eight sections are: vitality, physical functioning, bodily pain, general health perceptions, physical role functioning, emotional role functioning, social role functioning and mental health.

4.11.1.6 FACIT-Fatigue

The FACIT-Fatigue scale is a 13-item, symptom-specific subscale of the FACIT scales.13 Lower values of the FACIT-Fatigue score denote higher fatigue (score range, 0 to 52). Cella et. Al. validated a brief measure of fatigue in rheumatoid arthritis (RA), the Functional Assessment of Chronic Illness Therapy (FACIT) Fatigue Scale. The FACIT Fatigue was tested along with measures previously validated in RA: the Multidimensional Assessment of Fatigue (MAF) and Medical Outcomes Study Short-Form 36 (SF-36) Vitality. The FACIT Fatigue showed good internal consistency (alpha = 0.86 to 0.87), strong association with SF-36 Vitality (r = 0.73 to 0.84) and MAF (r = -0.84 to -0.88), and the ability to differentiate patients according to clinical change using the American College of Rheumatology (ACR) response criteria (ACR 20/50/70). This suggests that the FACIT Fatigue is a brief, valid measure for monitoring this important symptom and its effects on patients with RA.

4.11.2 Biopsy Assessment

The Pre and Post Biopsy Assessment Form is used to assess tolerability of biopsy procedure. The form will assess joint pain, stiffness, swelling as well as post-biopsy adverse events and additional analgesics used.

4.11.3 Imaging Assessments

Patients will have plain x-rays and ultrasound assessments of disease activity and joint damage and will be related to the secondary outcome measures in this study.

Arrangements will be made to facilitate the transfer of x-ray images and US assessment images from participating sites to the R4-RA Trials Office on a 6 monthly basis.

X-rays

Plain radiographs of the hands and feet will be recorded at baseline, 24, 48 and 96 weeks follow up and will be scored centrally by the van der Heijde/Sharp scoring system. X-rays should be taken separately for right and left sides of hand/feet. The standard NHS templates should be used. Plain X-rays of hands and feet do not need to be taken if the patient has already had them done within 8 weeks of the Baseline visit.

A chest x-ray must be performed as per routine screening for tuberculosis prior to biological therapy (depending on local guidelines). If a chest x-ray is required as per local guidelines this must be done at the screening visit to confirm the patient's eligibility, unless a chest x-ray has been done in the preceding 3 months of the screening visit and the patient must not have had any pulmonary symptoms since then.

Ultrasound

An Ultrasound assessment will be performed by a trained Rheumatologist at biopsy, baseline, 4, 12, 16, 24, 36, 48, 72 and 96 weeks follow up. Images will be acquired and scored centrally for Doppler signal (score of 0 – 3) and synovial thickness (score of 0 – 3) within a limited joint set. The core US data set is described in the 'R4-RA Trial US Manual'. Additional joints may be scanned at the local centres discretion.

Due to variation amongst Rheumatology departments with regards to resources and expertise to perform ultrasound assessments these will be optional for the purpose of this trial. Any such opt outs will be documented as part of the site set-up and initiation procedures for all participating sites.

4.11.4 Laboratory Assessments

Routine laboratory bloods for safety will be taken as per routine clinical care for patients receiving Rituximab or Tocilizumab.

4.11.4.1 Peripheral Blood analysis

Lab: Local site laboratory – The following blood tests will be performed at visits as per the study visit schedule (section 4.9): FBC, urea, creatinine, electrolytes, liver function tests, ESR, CRP, total cholesterol, HDL, LDL, triglycerides. These investigations will be performed at the local site laboratory.

Immunoglobulins must be tested for all patients at the screening visit and then subsequently only for patients receiving Rituximab. These should be repeated prior to every cycle of Rituximab. This includes patients switching from Tocilizumab to Rituximab. (Please refer to study visit schedule, section 4.9). Immunodeficiency panel is not mandatory, but should be carried out as per local guidance.

Study specific bloods
Lab: QMUL, Experimental Medicine and Rheumatology
In addition, study specific bloods will be taken as follows;

Biopsy visit (visit 2), Visits 7, 15, 17
Samples drawn in the order:
1. Four (9.0ml) Heparin (green top)
2. One (9.0ml) serum (red top)
3. Two PAXgene RNA* (8.5ml total volume, 2.5ml blood)
(Note: RNA taken at biopsy visits)

Visits 3a*, 4, 5, 9, 9a*, 10, 12
Samples drawn in the order:
1. Four (9.0ml) Heparin (green top)
2. One (9.0ml) serum (red top)

*Extra study specific bloods will be taken at visits 3a and 9a for Rituximab patients only, as indicated on study visit schedule (section 4.9).

Important Note: Participants may be subject to variation to the study specific bloods schedule as detailed in the study visit schedule foot note (section 4.9).

Further details of blood sample requirements, handling, transfer and storage are contained in the R4-RA Trial Sample Collection & Shipment SOP.

Blood and synovial tissue samples collected as part of the R4-RA trial will be used in the following types of analyses: FACS analysis, Functional B cell studies and peripheral blood autoantibody and cytokine production, ELISA/WB, Next Generation Sequencing & Validation and transcriptomic analysis in the Experimental Medicine and Rheumatology (EMR) Laboratory. Samples may be sent to other laboratories for analysis, it will be ensured that appropriate agreements are in place for this.

4.11.5 Synovial biopsies and tissue analysis

Synovial biopsies will be performed at baseline (mandatory). Further optional biopsies may be offered: week 16, at any subsequent visit prior to week 48 if the patient switches treatment or otherwise at week 48, and week 96. Synovial fluid will also be collected and stored concurrently with each biopsy whenever available. Tissue will be processed for paraffin embedding, snap frozen for histological analysis and immersed in RNA-Later for later RNA extraction.

Histopathological characterisation

B Cell Score (used for patient stratification and randomisation):
Lab: NHS Pathology Laboratory, Barts Health NHS Trust – The level of B cell infiltration in synovial tissues is based on a 5-point scale: 0-4 depending on the increasing number of positively stained cells calibrated against a standardized atlas (Appendix II). Accordingly synovial biopsies will be categorized in B Cell Poor (0-1), B Cell Rich (2-3) and Germinal Centre (GC) Rich (4). GC will be further identified by the presence of CD21 +ve follicular dendritic cells (FDC) networks. The biopsy tissue processing, embedding, staining and slide scanning will be undertaken by an accredited NHS histopathology department at The Royal London Hospital. Samples will be stored at Core Pathology until transfer to QMUL, EMR for long term storage.. Further details can be found in the separate workflow ‘R4-RA Trial processing and cutting synovial biopsy SOP’.

In some circumstances, processing and review of biopsy samples may be undertaken at the EMR laboratory, QMUL.

This semi-quantitative scoring method will be compared against an alternative Digital Image analysis scoring method to optimise B cell poor/B cell rich classification.

Analyses being conducted will be detailed in more specific laboratory analysis plans. Samples collected during this project will be stored in a tissue bank at the end of the project and will be used in future research.

4.12 **End of Trial Definition**

The end of the trial will be triggered when the last recruited patient completes the treatment phase of the trial at 48 weeks + 30 days (post-treatment Safety Follow-up Visit/ phone call) (Last Patient Last Visit LPLV). Visit 16 (72 weeks) and Visit 17 (96 weeks) will be completed for patients if these visits fall within the data collection period of the trial. This will be for patients recruited in the earlier stages of recruitment. Sites will be notified of the end of the data collection period (this will be confirmed when recruitment is completed).

Up to an additional 6 months may be added to this timeline to allow time for completion of sample processing and image scoring as required.
The end of trial declaration will be submitted within 90 days of the end of trial definition and this will mark the end of trial data and sample collection, laboratory work and image scoring. The clinical study report will be submitted within 12 months of the end of trial definition.

4.13 **Management of laboratory abnormalities and infections**

Based on risk-benefit assessment, the investigator must decide what action should be taken to ensure the safety of the provided treatment. This includes temporary interruption or cessation of IMPs and/or concomitant treatment, repeat or unscheduled laboratory assessment and reporting of AE/SAE when applicable.

4.13.1 Bone marrow toxicity

Neutropenia- ANC decrease to <1000/mm3 should result in treatment interruption until ANC rise to >1000/mm3. In the case of Tocilizumab, treatment is resumed, when ANC increases to >1000/mm3, at 4mg/kg and is increased to 8mg/kg as clinically appropriate. Treatment should be ceased and patient withdrawn from the study, if ANC < 0.5 x 10^9/l (see section 4.14).

Thrombocytopenia- Platelet decrease to <100,000/mm3 should result in treatment interruption until platelets increase to > 100,000/mm3. In the case of Tocilizumab, treatment is resumed, when platelets increase to >100,000/mm3, at 4mg/kg and is increased to 8mg/kg as clinically appropriate. Treatment should be ceased and patient withdrawn from the study, if platelets < 75 x 10^3/μl (see section 4.14).

4.13.2 Liver enzyme abnormalities

In ALT or AST elevations up to 3 x ULN, the dose of the concomitant medication (e.g. Methotrexate) should be modified whenever appropriate and suitable investigations undertaken. In the case of Tocilizumab, persistent increases of ALT or AST in this range should lead to dose reduction to 4mg/kg or interruption, until resolution. Dose interruption is recommended if ALT or AST >3 x ULN, and the aforementioned recommendations are followed when ALT or AST decrease to 1-3 x ULN. For persistent increases of ALT or AST >3 x ULN, as well as ALT or AST elevation >5 x ULN, treatment discontinuation is recommended (see section 5.14).

4.13.3 Infection

Patients must be monitored closely for signs and symptoms of infections including tuberculosis. Suspicion of infection should lead to treatment interruption if indicated. Study treatment should be resumed after resolution of the infection and regardless of when antibiotics have been stopped, at physician's discretion.

4.13.4. Reporting of laboratory abnormalities

Please record any abnormal laboratory results as AE if it is deemed clinically significant or requires intervention or interruption of the IMP. If it was considered serious please report the event as SAE/SUSAR.

4.14 Subject Withdrawal (from trial treatment)

Participants may be withdrawn from trial treatment if they are intolerant to the therapeutic product, experience toxicity related side-effects or inter-current illness necessitating cessation of the therapy at any time throughout the trial at the physician's discretion.

Specifically, the following criteria will necessitate premature withdrawal from trial treatment of a study participant:

- Suspected progressive multifocal leukoencephalopathy (PML)
- ALT or AST > 5 x ULN (or persistently >3x ULN)
- ANC < 0.5 x 10^9/l
- Platelet count < 75 x 10^3/μl
- Receipt of live vaccines
- Pregnancy

Subjects may withdraw consent for any reason at any time without prejudice to their normal care. Patients withdrawing from the study will continue to be monitored and managed within their routine Rheumatology clinic by their named consultant. Withdrawn trial subjects will not be replaced. Withdrawal of consent may be regarded as a withdrawal from trial medication or any other components which form part of the Informed Consent Form signed by the participant.

4.15 Data Collection and Follow up for Withdrawn Subjects

At the time of withdrawal, a full efficacy and safety evaluation should be performed if patient consents. Treatment cessation and reason for discontinuation should be documented on the applicable CRF and medical records. On-going data collection requirements for patients who withdraw from the trial prematurely are as follows:

- If the patient withdraws consent to any further participation in the trial the Treatment Cessation CRF should be completed immediately. A final assessment should be undertaken if the patient is present and consents to this as per the Early Withdrawal visit (see Study Visit Schedule) and the Treatment Cessation CRF should be completed. No further data is to be collected.

- If the patient ceases trial treatment before the Visit 7 (16-week assessment), the Treatment Cessation CRF should be completed immediately. The patient will continue to attend follow-up visits at 16, 24, 48, 72 and 96 weeks. At each visit, assessments should be as per Early Withdrawal visit (see Study Visit Schedule) and the Early Withdrawal Follow-up CRF should be completed each time.

- If the patient ceases trial treatment after the 16-weeks' assessment, the Treatment Cessation CRF should be completed immediately. The patient should continue to be followed-up and data collected according to protocol, unless participant withdraws consent for this. The applicable visit assessments and CRF should be completed at each subsequent visit.

Details of commencement of any further treatment outside of the trial will be recorded for all patients who withdraw prematurely from the trial.

5 PHARMACOVIGILANCE

5.1 Adverse Event (AE)

An AE is any untoward medical occurrence in a subject to whom a medicinal product has been administered, including occurrences which are not necessarily caused by or related to that product. An AE can therefore be any unfavourable and unintended sign (including an abnormal laboratory finding), symptom or disease temporarily associated with the use of an Investigational Medicinal Product (IMP), whether or not considered related to the IMP or to trial related procedures.

5.2 Adverse Reaction (AR)

An AR is any untoward and unintended response in a subject to an Investigational Medicinal Product (IMP), which is related to any dose administered to that subject. All adverse events judged by either the reporting investigator or the Sponsor as having a reasonable causal relationship to a medicinal product qualify as adverse reactions. The expression reasonable causal relationship means to convey in general that there is evidence or argument to suggest a causal relationship.

5.3 Serious Adverse Event (SAE)

An SAE must fulfil at least one of the following seriousness criteria:

Is fatal – results in death
Is life-threatening
Requires inpatient hospitalisation or prolongation of existing hospitalisation
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
Results in any other medically important event

Note: The following events are not considered as SAEs for the R4-RA trial

- Pregnancy (however it is an event that requires monitoring and follow up) – see section 5.5.6
- Procedures that were planned prior to the screening visit (although this does not exclude any complications post-procedure)
- Pre-existing conditions prior to the screening visit <u>unless the condition has worsened</u>

Note: “The following event **is** considered a SAE for the R4RA trial:
-Elective surgery at any time which is related to, or has resulted from, any new or worsening condition”

Serious Adverse Reaction (SAR)

An SAR is an adverse reaction which fulfils at least one of the following seriousness criteria:

Is fatal – results in death
Is life-threatening
Requires inpatient hospitalisation or prolongation of existing hospitalisation
Results in persistent or significant disability/incapacity
Is a congenital anomaly/birth defect
Results in any other medically important event

Suspected Unexpected Serious Adverse Reaction (SUSAR)

The definition of a SUSAR is any serious adverse event related to an IMP that is both suspected to be related to the IMP and unexpected. In this case the event is not outlined in the Summary of Product Characteristics (SmPC).

5.4 Investigators Assessment

Seriousness
The Principal Investigator (PI)* responsible for the care of the patient, is responsible for assessing whether the event is serious, according to the definitions given in section 5.3.

Causality
The PI* must assess the causality of all serious adverse events/reactions in relation to the trial treatment according to the definition given. If the SAE is assessed as having a reasonable causal relationship, then it is defined as a SAR.

Expectedness
The PI* must assess the expectedness of all SARs according to the definition given. If the SAR is unexpected, then it is a SUSAR. Expectedness must be assessed with reference to the relevant SmPC (Rituximab or Tocilizumab) for the medication being administered to the patient.

Severity
The PI* must assess the severity of the event according to the following terms and assessments. The intensity of an event should not be confused with the term "serious" which is a regulatory definition based on patient/event outcome criteria.

Mild: Some discomfort noted but without disruption of daily life
Moderate: Discomfort enough to affect/reduce normal activity
Severe: Complete inability to perform daily activities and lead a normal life

*or in the absence of the PI, an authorised medic within the research team who has been delegated this role,

Notification and reporting Adverse Events or Reactions
If the AE is not defined as SERIOUS, the AE is recorded in the study file and the participant is followed up by the research team. The AE is documented in the participants' medical notes (where appropriate) and the CRF.

AEs and SAEs should be recorded from the time that the first trial specific assessment/procedure is undertaken (screening visit), and then subsequently at follow-up visits throughout duration of trial treatment. Participants should be advised to notify the trial site of any untoward medical events as soon as possible, even if this is outside of their normal visit schedule.

SAEs should continue to be reported following the same procedures up to 48 week visit where trial treatment ceases or earlier if the participant withdrew from trial treatment prematurely, **and for a further 30 days post-trial treatment (IMP)**. AEs and SAEs will continue to be recorded after this time and until the patient reaches their final visit. Events will be documented in the participants' medical notes (where appropriate) and the CRF, however such events will not be reported in an expedited fashion.

5.5 Notification and Reporting of Serious Adverse Events/SUSAR

5.5.1 Serious Adverse Events

All Serious Adverse Event (SAEs) will be recorded on the SAE eCRF at the local trial site.

Causality must be assessed and completed by the PI or other delegated person(s). The person assessing causality must sign a paper copy of the SAE CRF. The CRF must be sent to the R4RA trial office **immediately and within 24 hours** of becoming aware of the event. The R4RA trial office will review the SAE CRF for data completeness.

The CI will assess the SAE and may send queries back to the reporting local site as applicable.

All SAEs received at the R4-RA trial office must be reported to the Joint Research Management Office (JRMO) at QMUL **immediately and within 24 hours** of the site becoming aware of the event. Nominated co-investigators will be authorised to assess causality on the SAE forms in the absence of the CI at the R4-RA trials office. The JRMO office, QMUL, as sponsor, will be informed of these nominated co-investigators who may sign in the absence of the CI.

5.5.2 Suspected Unexpected Serious Adverse Reactions

Suspected Unexpected Serious Adverse Reactions (SUSARs) that occur during the trial should be dealt with in the same way as all other SAEs. The reporting PI, or other delegated person(s), will need to complete the SAE report forms to be sent to the relevant national competent authority.

The JRMO, QMUL, as the sponsor, has a legal obligation to report UK-based SUSARs to the MHRA within 7 days of the event (for fatal or life-threatening SUSARs) and any follow-up information within a further 8 days, or 15 days for all other SUSARs. For UK sites the Trials office and CI are delegated the responsibility of reporting SUSARs to the Main Research Ethics Committee. Outside of the UK expedited safety reporting according to the relevant national guidelines will be delegated to the research team in the country in which the SUSAR or SAE occurred, with sponsor oversight. If warranted, an investigator alert may be issued, to inform all investigators involved in any study with the same drug (or therapy) that this serious adverse event has been reported.

The first SAE CRF for an event and any subsequent follow up of Serious Adverse Event CRFs and CIOMS forms (where applicable), together with the fax/email confirmation sheet must be kept with the local Investigator File at the study site.

5.5.3 Urgent Safety Measures

The CI may take urgent safety measures to ensure the safety and protection of the clinical trial subjects from any immediate hazard to their health and safety, in accordance with Regulation 30. The measures should be taken immediately. In this instance, the approval of the Licensing Authority Approval prior to implementing these safety measures is not required. However, it is the responsibility of the CI to inform the sponsor, Main Research Ethics Committee (via telephone) and the MHRA (via telephone for discussion with the medical assessor at the clinical trials unit) of this event immediately.

The CI (or delegated persons) has an obligation to inform both the MHRA and Main Ethics Committee in the UK in writing within 3 days, in the form of a substantial amendment. For non-UK sites, the requirements for urgent safety measure reporting to the national competent authority and local ethics committees (or equivalent) will be delegated to a lead research team in that country. The sponsor (JRMO) must be sent a copy of the correspondence with regards to this matter.

5.5.4 Development Safety Update Reporting (DSUR) and Annual Progress Report

The CI will carry out a risk-benefit analysis of the IMPs encompassing all events having arisen on the trial. The Development Safety Update Report (DSUR) will be sent by the CI to the REC and MHRA (the date of the anniversary is the date on the “notice of acceptance letter” from the MHRA) using the DSUR form. The DSUR will be submitted via CESP by the Trials Office to the non-UK national competent authorities and to their Ethics committees (if required) by the lead research team in that country.

The CI will send the Annual Progress Report to the main REC using the NRES template (the anniversary date is the date on the MREC "favourable opinion" letter from the MREC) and to the sponsor.

5.5.5 Overview of the Safety Reporting and Pharmacoviligance responsibilities

The CI has the overall pharmacovigilance oversight responsibility. The CI and R4-RA trial office have a duty to ensure that pharmacovigilance monitoring and reporting is conducted in accordance with the sponsor's requirements.
Further details of the process for reporting SAEs/SUSARs are detailed in the separate 'R4-RA Trial: SAE reporting for Investigators SOP'.

5.5.6 Pregnancy

If a patient becomes pregnant whilst involved in a CTIMP, it is not considered to be an SAE or an AE. However, it is an event that requires monitoring and follow-up. If a patient, or his partner, becomes pregnant whilst enrolled in a CTIMP in which the foetus has been exposed to an investigational medicinal product, immediate reporting to the sponsor is required (within one working day of the PI/CI becoming aware of the event) using a JRMO pregnancy template form. The CI/PI has the responsibility to ensure that the pregnancy form is completed and sent to the sponsor within the agreed timelines.

In the event of pregnancy, the patient must be withdrawn from the trial and the procedures for premature withdrawal should be followed as described in section 4.14.

The PI/CI also must follow up the pregnancy until delivery as well as monitoring the development of the newborn for 1 month after birth. Any events that occur during this time that could be considered to be a SAE must be reported to the sponsor in line with section 5.5.21, utilising the sponsor SAE reporting form.

6 STATISTICAL CONSIDERATIONS

6.1 Primary Endpoint Efficacy Analysis

The primary endpoint is the treatment response assessed using the Clinical Disease Activity Index (CDAI) at 16 weeks on the B cell poor population. Section 4.11.1.1, defines treatment response/failure criteria.

The primary analysis will focus on whether there is a superiority of Tocilizumab over Rituximab in histologically defined 'B cell poor' patients.

6.2 Secondary Endpoint Efficacy Analysis

1. Patients deemed treatment failures at 16 weeks, will be switched to the other therapeutic option. Such patients will be considered a new patient starting at week 0 with treatment response assessed again at 16 weeks for primary response. Treatment difference before and after switch will be compared in B cell poor and B cell rich.

2. For the B-cell rich synovial pathotypes, we aim to show non-inferiority of Rituximab compared to Tocilizumab. The same analysis as for the primary endpoint will be repeated.

For the following endpoints, the treatment difference will be assessed separately in B cell poor, B cell rich and in the switches:

3. Area under the curve (AUC) of mean improvement in DAS28 over time between 0 and16 weeks and between 0 and 48 weeks
4. Percentage of patients with low disease activity (DAS28 < 3.2) at 16, 24, 36, 48, 96 weeks
5. Percentage of patients in remission (DAS28 < 2.6) at 16, 48 and 96 weeks
6. Percentage of patients with a low clinical disease activity index score (CDAI) at 16, 48 and 96 weeks
7. Mean % change in DAS28 between baseline and 16, 48 and 96 weeks

8. Mean % change in SF-36 score between baseline and 16, 48 and 96 weeks
9. Mean % change in clinical disease activity index score (CDAI) between baseline and 16, 48 and 96 weeks
10. Mean change in HAQ score between baseline and 16, 48 and 96 weeks
11. Change in Fatigue score between baseline and 16, 48 and 96 weeks
12. Serious adverse events over 12 months; the rate of serious adverse events in the 16 week period following a switch from one technology to the other will be compared
13. Mean change in erosive score by the van der Heijde/Sharp scoring system at baseline and week 24. .
14. Reduction in US 2D grey scale and power Doppler signal at Baseline, 16 and 48weeks.
15. Mean change in synovial immune cell infiltrate determined immunohistologically (C20, CD68, CD138, CD3) between baseline, 16 and 48 weeks
16. Mean change in synovial gene expression between baseline, 16 weeks and 48 weeks
17. EULAR response based on DAS28 (good and moderate responder/non-responders)

6.3 **Exploratory end points**

Germinal Centre pathotypes will constitute an exploratory component to the trial as insufficient power will be generated to show a significant difference in clinical response between each treatment.

1. Association between disease outcome, treatment group and synovial histology
2. Association between disease outcome, treatment group and Ultrasound measure of inflammation
3. Association between disease outcome treatment group and Disability

6.4 **Safety Endpoints**

There are no safety endpoints however data on AEs and SAEs will be collected throughout the trial both in relation to the IMPs and trial conduct (eg synovial biopsy procedure).

6.5 **Sample Size**

The initial sample size was calculated based on a pilot cohort of 27 anti-TNF resistant patients where 67% were B cell poor, 18% B cell rich, and 15% germinal centre positive. After recruitment of the initial 67 patients of the R4RA study, we revised the proportions based on the observed pathotype proportions (60% B cell poor, 35% rich and 5% GC) and dropout rate. Clinical trial data suggests ACR20 response proportions of around 50%-60% for both Rituximab (REFLEX study, Arthritis and Rheumatism 2006) and Tocilizumab (RADIATE study, Ann Rheum Disease 2008). Our pilot study further demonstrates response rates of 25% in germinal centre positive patients, 80% in the B cell rich group and 22% in the B cell poor group. Based on observed dropout rate in the first 67 patients, sample size will assume 5% dropout rate. The numbers required, with these assumptions, are outlined in the table below. In addition, in order to estimate a total sample size, 10% was added to account for patients that have an unknown pathotype.

Power for primary analysis	**B cell poor**	**B cell rich**	**GC**	**Total**	**Addition of 10% to account for unknown pathotype**
90%	82 (86)	48 (51)	8 (8)	138 (145)	160
80%	62 (65)	36 (38)	5 (5)	103 (108)	119

Please note that these assumptions are made based on the proportions of the pathotypes in the first 67 patients recruited to the trial.

*Values in brackets show values adjusted for 5% dropout

1.For the B cell poor patients the aim is to show whether or not Tocilizumab is superior to Rituximab assuming response rates of 55% and 20% respectively. In order to have 90% power using a two-sided chi-square test of proportions with alpha of 0.05, one would need 82 patients in total (41 per arm). In order to have 80% power using a two-sided chi-square test of proportions with alpha of 0.05, one would need 62 patients in total (31 per arm). In the event that the true response rates are 55% and 25%, 82 patients would give 79% power (62 patients will give 67% power).

2. The emerging data of 67 patients from the R4RA trial suggests a dropout rate of 2.1%. We will use 5% in the calculation. By the time the number of B cell poor patients evaluated at 16 weeks and those who have been randomised but have not yet completed 16 weeks in the trial is between 62 and 82 (80 and 90% power) we predict that we will have recruited between 36 and 48 B-cell rich patients. 3. Fewer than 36 B cell rich patients will provide insufficient power to show non-inferiority even assuming that the true efficacy of Rituximab is slightly better than Tocilizumab in B-cell rich patients (If the true response rates are 80% for Rituximab and 55% for Tocilizumab, then 36 patients would give 68% power to show that the lower bound of the relative risk was at least 0.8. With 48 patients, the power would reach 81%). The plan is to test to see whether the relative effects of Rituximab and Tocilizumab differed between the B cell rich and B cell poor participants. Under the assumption that the response rates are 55%, 20%, 55% and 80% in B cell poor TOC, B cell poor RTX, B cell rich TOC and B cell RTX respectively, the power to detect an interaction between B cell type and treatments would be 95% with 82 B cell poor and 48 B cell rich patients, and 86% with 62 B cell poor and36 B cell rich patients.

4. For Germinal Centre, we hypothesize that patients will do poorly in both arms. The plan is to study the change in biomarker in synovial biopsies before and after treatment. If it is true that patients with Germinal Centre do poorly, and if one treatment breaks up the Germinal centre making patients B cell rich, then those patients may respond to treatments better subsequently. By the time we have recruited between 62 and 82 B-cell poor patients and between 36 and 48 B cell rich patients, we should have recruited between 6 and 8 Germinal Centre patients. If the proportions of Germinal Centre patients that had become B-cell rich at six months were 5% and 60% in the two arms, 8 GCs gives power of 10% (6 GCs gives 4% power) using a two-sided Fischer test of proportions with alpha of 0.05. The proportions 5% represents little or no change in germinal centres which is what we assume would happen in the absence of treatment. The 60% change represents a drug which is able to break up just over half of the germinal centres which is something one would not wish to miss. We would also use this to provide pilot data on the clinical response to treatment at 12 months comparing: “Tocilizumab followed by Rituximab for patients who do not respond to Tocilizumab “to “Rituximab followed by Tocilizumab for patients who do not respond to Rituximab”

In summary, recruitment will stop in December 2017 or when at least 86 B-cell poor and at least 51-B-cell rich patients have been recruited (numbers adjusted for 5% dropout and in order to achieve 90% power).* When we have recruited this number of B cell poor and B cell rich patients, it is estimated that we will have 8 Germinal Centre patients. In addition, the total sample size has been increased by 10% to account for the unknown pathotype.

*Based on assumptions of B cell poor vs B cell rich proportions as described above, it is estimated that approximately 160 patients will be required to achieve 90% power.

The Trial Steering Committee (TSC) and Trial Management Group (TMG) will monitor recruitment (with oversight from the Data Monitoring & Ethics Committee (DMEC)).

6.6 **Statistical Analysis**

All statistical tests will be two-sided and use alpha of 5%; 95% confidence intervals will be provided for estimated quantities.

1.The primary outcome measure will be the binary clinical endpoint based on the change in the mean CDAI score over 16 weeks. Non-response will be a CDAI response of less than 50% in comparison to baseline.
2.For the randomised comparison of Rituximab versus Tocilizumab in B-cell poor patients, the primary endpoint will be analysed (by intent to treat) using the chi-squared test for the difference between two proportions.
3.For non-randomised comparisons between subgroups identified by (presence or absence of) B-cells in synovial biopsies, we will use the Fisher exact test comparing (i) response to Rituximab in B-cell poor patients compared to B-cell rich (without germinal centre). There will be no adjustment for potential risk modifiers because, a priori, we know of no such factors in the trial population. (Inclusion and exclusion criteria to this trial ensure that the patients are clinically homogeneous). The definition of B-cell status will be clearly defined before the start of the trial.
4.A test of interaction between treatment and B-cell status (rich versus poor, excluding germinal centre) will be based on a likelihood ratio tests between nested logistic regression models.
5.Patients who fail to respond during the first 16 weeks and cross-over treatment will also provide evidence regarding the efficacy of the two treatments and the predictive significance of B-cells in synovial biopsies. The post cross-over results will be combined with the pre-cross over results in a secondary analysis stratified by pre/post cross-over. Such analyses will be particularly important for comparison of treatments in B-cell rich patients (where the difference in treatment efficacy is hypothesised to be modest) and in germinal centre patients (in whom it is hypothesised that initial treatment may break up the germinal centre and allow a second biological to be effective). The additional power obtained from such a combined analysis has not been taken into account here.

7 DATA HANDLING & RECORD KEEPING

7.1 Confidentiality

The CI and participating trial sites have a responsibility to ensure that patient anonymity is protected and maintained. They must also ensure that their identities are protected from any unauthorised parties. Information with regards to study patients will be kept confidential and managed in accordance with the Data Protection Act, NHS Caldicott Guardian, The Research Governance Framework for Health and Social Care and Research Ethics Committee Approval.

The CI and trial sites must adhere to these parameters to ensure that the Patient's identity is protected at every stage of their participation within the study. To ensure this is done accordingly, each patient, at time of consent must be allocated a unique screening number by either the PI or a member of the trial team before undergoing any screening procedures. The patients initials (the first letter of their first name and the first letter of their last name) should be used as a means of pseudo-anonymising parameters. This information should be kept on a screening log, which should be updated accordingly throughout the study. Once the patient has completed screening procedures and is enrolled onto the study, the patient will be allocated a randomisation number by the PI (from a master randomization list).

The co-ordinating site will not hold any patient identifiable data. All clinical data will be stored in an encrypted format on the database, only viewable in a readable format by local trial staff and only for participants recruited at their site. The Chief Investigator is the 'Custodian' of the data collected. Patients will be consented and will not own the results generated using the sample/s and data collected and in addition will not be entitled to any interest in or share of any profit that might arise from research using the sample/s or data. The patients will be anonymised with regards to any future publications relating to this study.

7.2 Data Collection

Data collection will be in the form of completing electronic CRFs via the trial database to record all the required assessments at each study visit.

7.3 Record Retention and Archiving

During the course of research, all records are the responsibility of the Chief Investigator and must be kept in secure conditions. When the research trial is complete, it is a requirement of the Research Governance Framework and QMUL Policy that the records are kept for a further 20 years. For trials sponsored by QMUL site files from other sites must be archived at the participating site.

7.4 Compliance

This trial will be conducted in accordance with the principles of Good Clinical Practice (GCP) as laid out in the EU directive and The Medicines for Human Use (Clinical Trials) Regulation 2004, and its amendments.

In addition, internal auditors and Competent Authority inspectors will be allowed access to CRFs, source documents and other trial files to evaluate the trial. Audit reports will be kept confidential.

7.5 Clinical Governance Issues

7.5.1 Ethical Considerations

The trial will be performed in accordance with the recommendations guiding ethical research involving human subjects adopted by the 18th World Medical Assembly, Helsinki, Finland, 1964, amended at the 48th General Assembly, Somerset West Republic of South Africa, October 1996. Informed written consent will be obtained from the patients prior to randomisation/registration into the study. The right of a patient to refuse participation without giving reasons must be respected. The patient must remain free to withdraw at any time from the study without giving reasons and without prejudicing his/her further treatment.

The study will be submitted to and approved by a main Research Ethics Committee (REC). Changes in protocol that may increase the exposure to risk or present new risks to the patient, or may adversely affect the validity of the study, must be approved in writing by the sponsor and then the REC before the change is implemented. These changes are usually presented in the form of an amendment.

The study will be regularly reviewed by the in-house monitoring and ethics committee. This will be done to verify that data is being accurately recorded and documented. Further, the committee will routinely review study documents with an eye towards ensuring that the study protocol is accurately followed and GCP compliant.

7.6 Quality Control and Quality Assurance

7.6.1 Summary Monitoring Plan

On-Site Monitoring will be carried out on this trial. The trial monitor will perform the first monitoring visit as soon as possible after the first patient is randomised and aim to be performed within 1 month (+/- 2 Weeks) of the first patient being randomised at a site.

Monitoring visits will be performed a minimum of twice a year during recruitment and treatment period at approximately 6 monthly intervals (+/- 4 weeks).

The frequency of visits is detailed in the Monitoring Plan and may change (increase or decrease) depending on the issues raised during the trial (death, SAE, audit or inspections, site not recruiting). Any decrease in monitoring at a site will be approved by a member of the R4-RA trial office and the Sponsor.

Source Data Verification will be carried out as follows and as per Monitoring Plan.
100 % SDV will be performed on informed consent
100 % SDV will be performed on inclusion / exclusion criteria

SDV on all other data points will be described in the R4-RA Trial Monitoring Plan).

The following central facilities are utilised in this trial and will undergo yearly monitoring visits for the duration of their participation in the trial:

* EMR Laboratory
* Barts Health NHS pathology lab

Please See Monitoring Plan for further details of monitoring procedures. A summary of all monitoring activity for this study will be provided to the Sponsor every 3 months.

7.6.2 Audit and Inspection

Auditing: Definition "A systematic and independent examination of trial related activities and documents to determine whether the evaluated trial related activities were conducted, and the data were recorded, analysed and accurately reported according to the protocol, sponsor's standard operating procedures (SOPs), Good Clinical Practice (GCP), and the applicable regulatory requirement(s)."

This trial may be audited by the Sponsor, or the Competent Authority. Investigators are obliged to cooperate in any inspection.

7.6.3 Serious Breaches in GCP or the Trial Protocol

All investigators participating in the trial will promptly notify the Chief Investigator or Sponsor of a serious breach (as defined in Regulation 29A of the Medicines for Human Use (Clinical Trials) Regulations 2004 [Statutory Instrument 2004/1031], as amended by Statutory Instrument 2006/1928) that they become aware of. The CI is then responsible for notifying the JRMO (the sponsor) within 24 hours of becoming aware of a serious breach.
The Sponsor is responsible for notifying the licensing authority in writing of any serious breach of:
(a) The conditions and principles of GCP in connection with that trial; or
(b) The protocol relating to that trial, as amended from time to time in accordance with regulations 22 to 25, within 7 days of becoming aware of that breach.

A "serious breach" is a breach which is likely to effect to a significant degree:-
The safety or physical or mental integrity of the subjects of the trial; or the scientific value of the trial.

Participating centres should contact the R4-RA trial office or CI for further information.

7.7 Trial Committees

7.7.1 Trial Management Group (TMG)

The Trial Management Group normally includes those individuals responsible for the day-to-day management of the trial, such as the chief investigator, statistician, trial manager, research nurse, data manager. The role of the group is to monitor all aspects of the conduct and progress of the trial, ensure that the protocol is adhered to and take appropriate action to safeguard participants and the quality of the trial itself. The TMG will meet monthly.

7.7.2 Trial Steering Committee (TSC)

The role of a Trial Steering Committee will be to provide overall supervision of the trial and ensure that it is being conducted in accordance with the principles of GCP and the relevant regulations. There will be an independent Chair

Decisions about continuation or termination of the trial or substantial amendments to the protocol will be the responsibility of the Trial Steering Committee. The TSC will meet every 6 months and may take the form of a teleconference or face-to-face meetings.

7.7.3 Data Monitoring and Ethics Committee (DMC)

The role of a Data Monitoring Committee will be to review the accruing trial data and assess whether there are any safety issues that should be brought to participants' attention or any reasons for the trial not to continue. The Data Monitoring Committee is independent of both the investigators and the funder/sponsor. It will meet 6 monthly which may take the form of a teleconference or face-to-face meetings. It will make recommendations to the Trial Steering Committee. There will be an independent chair. Once recruitment is complete, and the study is in follow-up phase only the DMEC may not meet formally to review the study. Instead a reduced report with be sent to members for their information on a six monthly basis with a request for feedback.

7.8 Publication Policy

This is an investigator led trial; sponsored by the CI's substantive employers, QMUL. The data collected will not be used to license/ register any pharmaceuticals. Authorship of the final manuscript(s), interim publications, or abstracts will be decided according to active participation in the study design, trial management group and accrual of eligible patients. Contributing centres (and participating Investigators) will be acknowledged in the final manuscript. Representatives for the Sponsor will be added, as appropriate, as co-authors. No participant may present data from his/her centre separately from the rest of the trial results unless approved by the CI/R4-RA management group and the Sponsor.

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9 SUMMARY OF AMENDMENTS

* Substantial Amendment = SA, Non Substantial Amendment = NSA

Amendment No.	Details of amendment	Date approved by MREC	Date approved by MHRA
NSA_#1	Amendment to protocol and PIS in line with requests made by MHRA for approval of the study. This was submitted to the REC for their info.	29-Jan-13 acknowledged	21-Jan-13
NSA_#2	Revised study Visit schedule (CRF) as follows: - Study bloods moved from Visit 3 to Visit 2. - Study bloods no longer required at Visits 6, 8, 10, 11, 13, 14, 16 - Baseline US assessment no longer required - Immunoglobulins moved from Baseline visit to screening (required). Protocol was updated as part of SA_#1	As per SA_#1	As per SA_#1
SA_#1	Protocol: - Change to biopsy schedule and primary end point (24 weeks to 16 weeks) - Revision (reduction) of study blood assessments - Addition of use of PICs - Clarification of fourth unknown stratum for randomisation procedures - Clarification of SAE reporting period - Clarification of procedures for early withdrawal - Clarification of events not to be reported as SAEs - Clarification of treatment period and observation period - Clarification of permitted steroid use - Collection of new data fields; previous anti-TNF and total Chol, HDL, LDL, tryglycerides. PIS: - Less prescriptive information on trial hypothesis to reduce patient bias - Clarification of potential to switch medication from Weeks 16 to 48 - Clarification of treatment period and observation period and visit schedules - Clarification for treatment after trial has ended. - Inclusion of emergency contact details. Minor amendments notified as per NSA_#2. Other formatting changes, clarifications, corrections to the above documents.	14-May-13	29-May-13
SA_#2	- Addition of trial sites - Change of PI (Barts Health)	03-Sep-13	n/a
SA_#3	1. Expansion of synovial biopsy technique to allow use of arthroscopic biopsy as well as US guided needle synovial biopsy (as per current protocol) 2. Additional exclusion criteria (listed in revised protocol as exclusion criteria #4- Prior exposure to Rituximab or Tocilizumab for the treatment of RA 3. Amendment to exclusion criteria already listed to include latex allergy or allergy to any excipients of Rituximab *and Tocilizumab* (applicable for both trial IMPs under investigation.) 4. Clarifications to procedures for administration of IMPs (specifically Rituximab) 5. Relaxation of requirements/restrictions for corticosteroid use and parenteral corticosteroids during treatment *Additional text:* Note: Any injected joints should be excluded from the joint count assessment for 12 weeks following the injection.	10-Apr-14	02-May-14

	6. Amendment to requirements for routine bloods at screening and biopsy time points 7. Clarifications on treatment schedule for both IMPs, specifically clarification that Rituximab patients should be retreated with the treat to flare regime, and therefore will not switch medication based on CDAI response criteria at this stage. 8. Amendment to requirement for x-ray of hands and feet at Baseline visit. *Additional text:* Plain X-rays of hands and feet do not need to be taken if the patient has already had them done within 8 weeks of the Baseline visit. 9. Addition of instructions to conduct tender joint (TJC) and swollen joint count (SJC). *Please also note: additional text, section 4.6:* All joint assessments will be performed by a member of the local trial team who will be blinded to treatment allocation of all participants. *The joint assessor should also complete the VAS physician assessment component of the VAS Pain Score questionnaire.* 10. Extra study specific blood time point at week 28 and clarification of potential for change to study blood schedule (in line with any potential switch in trial treatment as per protocol). 11. Additional PAXgene RNA tube at Biopsy visit, Week 16, Week 48 and Week 96 time-points. 12. Amendment to criteria for Early Withdrawal and clarification that this refers specifically to treatment cessation 13. Clarification on procedures for data collection and follow up for Withdrawn Subjects (making distinctions between treatment ceased and/or full consent withdrawn) 14. Clarification of procedures for SAE reporting post cessation of treatment (either prematurely prior to week 48 or at week 48) 15. Additional secondary endpoints (omitted from previous versions of the protocol) The addition of these secondary endpoints can be regarded as points omitted from previous protocol versions. There are no changes to protocol with regards to time-points and procedures of x-ray of hands and feet and US assessments and the addition of these do not affect any previous statistical calculations within the protocol. 16. Clarification of no safety endpoints (not previously specified) Previous versions of the protocol did not confirm safety endpoint data so this has now been clarified. 17. APPLICABLE only to lead site (Mile End Hospital, Barts Health) Revision of optional biopsy time point so that, for any patient, who chooses to have any subsequent biopsy [beyond week 16 visit], a biopsy may be taken at such time that a patient switches treatment.		
SA_#4	Addition of trial sites (Southampton and Basildon)	21/10/2014	N/A
SA_#5	Addition of trial sites (Aintree/Liverpool and Southend)	26/11/2014	N/A
SA_#6	1. Addition of optional biopsy consent form 2. Protocol: Addition of faster infusion schedule for second and subsequent Rituximab infusion, as per Rituximab SmPC. 3. Protocol: Addition of a time point (within 4 weeks prior to Visit 3 Baseline) where restrictions apply for the use of corticosteroids. 4. Protocol: Hepatitis B screening has been made mandatory to be consistent with SmPC for Rituximab (updated on 23/05/2014). Exclusion criteria #11 amended to "Known HIV or hepatitis B/C infection. Hepatitis B screening test must be performed at or in the preceding 3 months of screening visit." 5. Protocol: Clarification on reporting of laboratory abnormalities to define how they should be reported as AE, SAE or SUSAR. 6. Protocol: Clarification on exclusion criteria #24. New wording: "24. Patients currently recruited to other clinical trial(s) involving an investigational medicinal product (except any observational follow-up periods not involving an IMP)." 7 Patient Information Sheet: description of indemnity was amended 8. Patient Information Sheet: Explanation on follow up after withdrawal was made clearer 9. Protocol: US time-points have been amended (the total of 10 time-points remains unchanged) 10. SmPC: Update on SmPCs for Rituximab (Text Revision 23/05/2014) and Tocilizumab (Text Revision 01/09/2014) 11. Addition of Pre and Post Biopsy Assessment Form Other minor formatting changes, clarifications, corrections to the above documents.	13/01/2015	09/01/2015

NSA_#3	Minor amendment to re-version patient questionnaires, to clarify 4 weekly visit schedules for Visit 4-15, and to update this summary of amendments table.	04-Feb-2015	N/A
SA#7	1. Addition of trial sites (Manchester, Bath, and Guys). 2. Change of PI at Homerton trial site (Change from Beena Hamed to Piero Reynolds)	17-Jun-2015	
SA #8	Addition of trial site (Leeds).	18-Aug-2015	
NSA#4	SmPC for study IMP (Tocilizumab) updated 24/04/2015.	As per SA#9	As per SA#9
SA_#9	1. Change of Sponsor Representative. 2. Change of follow-up period for some patients resulting in updates to the end of study definition, PIS and ICF. (Section 4.6, Section 4.12) 3. Update to sample size calculation (Section 6.5) 4. New document 'end of trial letter' for participants. 5. Clarifications to existing inclusion and exclusion criteria (Section 2.4.2 and 2.4.3) 6. Clarification that RF/CCP tests should be conducted at screening unless the tests have been done previously and do not need repeating as per local guidelines (Section 4.2) 7. Clarification that baseline assessments should be done within a +/- 7 day window (Section 4.5) 8. Clarification that X-rays must be performed as per routine screening for tuberculosis at screening (Section 4.9) 9. Removal of text regarding statins as patients will be managed as per routine care (Section 4.6) 10. Clarification the serum immunoglobulins must be performed at screening (unless done 8 weeks before) (Section 4.9) 11. Clarification that a patient deemed a non-responder at visit 7 (week 16) can switch treatment at their subsequent visit (Section 4.8) 12. Clarification that for visits 7 onwards a patient can switch treatment at the following visit (Section 4.11) 13. Addition of secondary endpoints (Section 6.2) 14. Other minor amendments to protocol deemed minor but of note as detailed in the Notice of Substantial Amendment Form: - Section 4.11.4- Updates to laboratory analysis section - Section 4.15 – Clarification that Treatment cessation CRF should be completed if a patient withdraws consent - Section 5.3- Re-wording of SAE section - Section 5.5.2- Information provided on SUSAR reporting for non-UK sites - Section 5.5.3- Information provided on Urgent Safety measured reporting for non-UK sites - Section 5.5.4- Clarification on DSUR submission in non-UK countries - Section 7.6- Some corrections and provisions for some flexibility to monitoring plan (instead referencing separate monitoring plan). - Section 7.7 - Clarifications to membership and management of the Trial Steering Committee and Data monitoring and Ethics Committee. Additional change to the PIS: -Section 7- Addition of sentence so sites can add where biopsy procedure will be performed (as some patients may go to another site for this procedure. Addition of UCLH as a PIC site.	29-Jul-2016	15-Aug-2016
SA#10	Submission of a poster for R4-RA recruitment Minor updates to End of recruitment letter due to extension to recruitment. Use of patient video (already approved for STRAP trial) for purposes of R4RA trial recruitment.	30-Aug-2017	N/A
SA#11	Pg 6, and sections 2.4.1, 6.5 -clarification that recruitment will stop in December 2017 or when at least 86 B-cell poor and at least 51-B-cell rich patients have been recruited, whichever comes first. Section 2.4.2 – additional clarification to inclusion criteria #4		

	Section 4.4 – clarification that randomisation procedure is also stratified by site (QMUL vs Other) Section 4.9 – addition to study visit schedule of RTX and TCZ dispensing episodes and additional footnotes Section 4.11.5 – clarification that the semi-quantitative scoring method will be compared against an alternative Digital Image analysis scoring method to optimise B cell poor/B cell rich classification. Section 4.12 – minor clarification to end of trial definition to allow additional 6 months (if required) for completion of laboratory and imaging work. Section 6.1 – minor clarification on primary endpoint to reflect Statistical Analysis Plan (no change to intended analysis) Section 6.2 – addition of 'main' secondary endpoint incorrectly listed in section 6.1 (Primary Endpoint) in error, with clarification that Treatment difference before and after switch will be compared in B cell poor and B cell rich. Minor clarifications to existing other secondary/exploratory endpoints. (There is no change to intended analyses). Additional secondary endpoint 'EULAR response based on DAS28 (good and moderate responder/non-responders)' Section 6.3 – re-wording of an existing exploratory endpoint to clarify 4 distinct endpoint questions. Previous wording was ambiguous in this respect. No change to intended analysis. Section 6.5 – additional clarification – 'Please note that these assumptions are made based on the proportions of the pathotypes in the first 67 patients recruited to the trial.' Section 7.7.3 – Clarification of DMEC meeting requirements once recruitment to the trial is complete and is in the follow-up phase.		