Optimal management of RA patients who require BIologic Therapy (ORBIT study)

Compound	Rituximab
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This study will be performed according to the Research Governance Framework for Health and Community Care (Second edition, 2006) and The Medicines for Human Use (Clinical Trials) Regulations, 2004 SI 2004:1031 (as amended) and WORLD MEDICAL ASSOCIATION DECLARATION OF HELSINKI Ethical Principles for Medical Research Involving Human Subjects 1964 (as amended).

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Funder

Arthritis & Rheumatism Campaign

Protocol Approval

Study Title: Optimal management of RA patients who require BIologic Therapy (ORBIT study)

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Date: 16th December 2009

Participating site

Site name: Gartnavel General Hospital, Glasgow

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Signature:

Date: 16th December 2009

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ABBREVIATIONS

AE	Adverse event
AUC	Area under the curve
BSR	British Society of Rheumatology
CCP	Cyclic Citrullinated Peptide
CRF	Case report form
DAS28	28 joint Disease Activity Score
DMARD	Disease-modifying antirheumatic drug
EC	Ethics Committee
EOW	Every other week
EULAR	European League Against Rheumatism
GP	General Practitioner
ICH GCP	International Conference on Harmonization of Good Clinical Practice
IVRS	Interactive voice randomisation service
LDAS	Low disease activity state
NICE	National Institute for Clinical Excellence
RA	Rheumatoid Arthritis
RF	Rheumatoid Factor
SAE	Serious adverse event
SMC	Scottish Medicines Consortium
SUSAR	Suspected Unexpected Serious Adverse Reaction
SOP	Standard Operating Procedure
TNF	Tumour Necrosis Factor
ULN	Upper Limit of Normal

STUDY SYNOPSIS

Title of Study:	Optimal management of RA patients who require BIologic Therapy (ORBIT study)
Study Centre:	Multi-centre
Duration of Study:	3 years
Objectives:	An open label randomised controlled trial comparing rituximab with anti-TNF therapy in biologic naïve patients over 12 months
Primary Objective:	To compare the efficacy and cost effectiveness of anti-TNF therapy and rituximab therapy in the treatment of 'biologic-naïve' patients with active rheumatoid arthritis.
Secondary Objectives:	➢ To prospectively evaluate the influence of mood on response to, and side effect profile from, anti-TNF and rituximab. ➢ To identify whether synovial immuno-histology at baseline predicts differential response to rituximab and anti-TNF therapy.
Study Endpoints	The primary outcome measure will be the mean change in DAS28 between 0 and 12 months
Methodology:	Randomised controlled trial
Sample Size:	302
Registration/Randomisation:	via IVRS
Inclusion Criteria	Patients with active RA who are eligible for biologic therapy according to BSR guidelines and are sero-positive for RF and/or anti-CCP antibodies
Exclusion Criteria	Patients will be excluded if they have any contraindication to anti-TNF therapy or rituximab therapy: ➢ women who are pregnant or breast-feeding ➢ unwillingness to use effective contraception ➢ history of or current inflammatory joint disease or autoimmune disease other than RA ➢ treatment with any investigational agent ≤ 4 weeks prior to baseline or < 5 half-lives of the investigational drug ➢ intra-articular or parenteral corticosteroids ≤ 2 weeks prior to baseline. ➢ active infection ➢ septic arthritis within a native joint within the last 12 months ➢ sepsis of a prosthetic joint within 12 months or indefinitely if the joint remains in situ ➢ known HIV or hepatitis B/C infection ➢ latent TB infection unless they have completed adequate antibiotic prophylaxis ➢ malignancy (other than basal cell carcinoma) within the last 10 years ➢ New York Heart Association (NYHA) grade 3 or 4 congestive cardiac failure ➢ demyelinating disease ➢ latex allergy or allergy to excipients in any of the study medications ➢ any other contra-indication to the study medications as detailed in their summaries of product characteristics
Product, Dose, Modes of Administration:	Rituximab 1g IV; etanercept 50mg/week s.c.; adalimumab 40mg eow (up to maximum 40mg/week in patients not receiving methotrexate) s.c.
Duration of Treatment:	12 months
Statistical Analysis	Statistical analysis will be performed by the Robertson Institute of Biostatistics, University of Glasgow. Study endpoints will be summarised by treatment group at each time point – that is, the primary analysis will compare the strategy of treating with anti-TNF first (before rituximab in the treatment sequence), versus the alternative strategy of using rituximab first. The primary analysis will be to compare the primary endpoint between study groups, using a linear regression

	model with adjustment for baseline DAS28, study centre and other variables used to stratify the randomisation. Linear regression models, with adjustment for stratification variables and baseline values as appropriate, will also be used to compare study groups with respect to secondary and exploratory outcomes. Logistic regression will be used for binary endpoints. Data transformations and bootstrapping methods will be considered for the analysis of continuous endpoints that do not meet distributional model assumptions.

STUDY FLOW CHART

Visit	Screening	Baseline	1	2	3	4	5	6	7	8	9	10	11	12
Month		0	1	2	3	4	5	6	7	8	9	10	11	12
Clinical examination	x													
Obtain informed consent	x													
Pregnancy test[#]		x												
RF/CCP[##]	x													
CXR[##]	x													
Mantoux/T-SPOT*	x													
Hep B/C**	x													
DAS28	x	x	x	x	x	x	x	x	x	x	x	x	x	x
VAS Pain score		x						x						x
Cost questionnaire		x						x						x
HAQ score		x						x						x
Assessor's global VAS		x						x						x
EQ5-D		x			x			x			x			x
HAD		x			x			x			x			x
FBC		x	x	x	x	x	x	x	x	x	x	x	x	x
U&E/LFT		x	x	x	x	x	x	x	x	x	x	x	x	x
CRP		x	x	x	x	x	x	x	x	x	x	x	x	x
Adverse events			x	x	x	x	x	x	x	x	x	x	x	x
Concomitant medication	x	x	x	x	x	x	x	x	x	x	x	x	x	x
Synovial biopsy[+]		x												
Blood for serum, RNA and genomic DNA		x			x			x						
Administration of study medication														
Etanercept		*50mg subcutaneously once weekly*												
Adalimumab		*40mg subcutaneously every second week (and up to 40mg/week if necessary in patients not receiving methotrexate)*												
Rituximab		*1000mg by intravenous infusion followed by a second 1000mg intravenous infusion 2 weeks later. Above course can be repeated after a minimum of 20weeks depending on response – max 3 courses in 12 months*												

* according to local guidelines for screening

** if not previously done

[#] in women of child bearing potential

[##] if not done in the preceding 6 months

[+] in a sub-group of patients

INTRODUCTION

Anti-TNF therapy has become an established part of the treatment of patients with rheumatoid arthritis (RA) who fail to have (or maintain) an adequate response to conventional disease modifying anti-rheumatic drugs (DMARDs) according to the BSR Biologics guidelines which have been approved by NICE [1,2] Other biologic drugs, such as rituximab, have been approved for use in the NHS in patients who have failed anti-TNF therapy.[3] Rituximab is also effective in patients who have failed conventional DMARDs but have not yet been exposed to anti-TNF therapy.[4] It is possible that rituximab is more or less effective than anti-TNF therapy in biologic naïve patients but head to head trials have not been carried out. Rheumatologists are faced with the question – which biologic should be used first?

All biologics are expensive, and the relative cost effectiveness of available therapies needs to be considered. NICE and the Scottish Medicines Consortium (SMC) are charged with providing guidance to the NHS about the use of biologic drugs, but it is recognised that there is a great deal of uncertainty associated with the health economic modelling that is the basis of NICE/SMC decisions. Currently, randomised controlled trials have shown that anti-TNF and rituximab therapy are both effective**.** Whilst the overall response rates appear similar, there were important differences between the trial populations which make comparisons between trials of limited usefulness, and the data are compatible with important clinical differences in efficacy. The financial risk that the NHS is exposed to is considerable: the cost of anti-TNF therapy is approximately £9-10,000 per annum; rituximab costs ~£3,500 per treatment course, which need to be repeated (on average) every 6-9 months giving an annual cost of £4700 - 7000. In Scotland, there were ~450 biologic-naive RA patients started on an anti-TNF drug in 2007 (personal communication) which translates to ~4-5000 patients starting anti-TNF therapy each year in the UK, at an annual cost of ~£40million. Were rituximab to prove be as effective in biologic-naive patients as anti-TNF therapy this could result in savings to the NHS of £9 - 20 million per annum, depending on the frequency of re-treatment with rituximab that was required. On the other hand, if anti-TNF therapy is more effective than rituximab therapy, it would be very important to have good evidence to inform NICE/SMC appraisals which might otherwise conclude from the current literature that rituximab affords a more cost-effective approach.

The proposed trial is a randomised controlled trial that will compare the efficacy and cost-effectiveness of two treatment strategies in patients who require biologic treatment according to the BSR guidelines: starting with anti-TNF therapy first, compared to the use of rituximab first. Treatment will be switched to the alternative technology in the event of toxicity, lack or loss of response. Treatment doses and schedules will be according to the current licensed doses of all medications; rituximab will be used in accordance with recent trials in biologic-naïve patients which is expected to form the basis of Roche's application for a license extension (personal communication).[5,6] A pragmatic approach to anti-TNF therapy will be taken: there are variations in the choice of anti-TNF drug (etanercept, infliximab or adalimumab) and there is no consensus (or evidence) that one is superior to another. This fact is recognised by NICE who recommends the use of anti-TNF therapy but has not identified an anti-TNF drug of choice. In the UK, the vast majority of patients are treated with one of the two sub-cutaneous preparations (etanercept or adalimumab) rather than infliximab for logistical reasons. Hence, patients enrolling in the trial and who are randomised to anti-TNF therapy will be treated with either adalimumab or etanercept, following discussion and advice from their rheumatologist. There is evidence that patients who are sero-negative for rheumatoid factor and anti-CCP antibodies are less likely to respond to rituximab therapy,[7] and the consensus is that such patients should be treated with anti-TNF therapy and will be not be eligible for the trial. Safety remains an important concern for patients and clinicians and all adverse events will be carefully recorded, although a trial of this size will not have the power to exclude clinically relevant differences between treatments in the rate of serious adverse events. The side effect profiles for anti-TNF and rituximab therapy differ, but both treatment modalities are associated with an increased risk of infection. In contrast some adverse effects are associated specifically with anti-TNF (e.g. demyelination) or rituximab (e.g. Progressive Multifocal Leucoencephalopathy) therapy. The safety of adding anti-TNF therapy to patients who remain B-cell depleted is important. The evidence to date suggests that there is no significant increase in the risk of serious infective complications in these patients,[8] but a comparison of the rate of adverse events in patients switching from rituximab to anti-TNF therapy will be compared to the rate seen in those switching form anti-TNF to rituximab.

In addition, co-existing depression is common in patients with severe RA and has been shown to significantly reduce patients' response to, and increase side effects from, anti-TNF therapy. It is not known whether a similar effect occurs with Rituximab. If the effect of pre-existing depression on response differs between anti-TNF and rituximab therapy, this could have a major impact on biologic choice for depressed patients in routine clinical care.

It is known that only a proportion of patients achieve remission or a low disease activity state (LDAS) with biologic therapy. Partial or non-response entails significant cost, encompassing an economic burden on the NHS and exposure to potential adverse events for the patient. Predicting those patients in whom clinical responses are most likely to occur would aid decision making for clinicians, reduce unnecessary adverse effects for patients and confer considerable health utility benefits. Patients who agree to participate in ORBIT will be asked to consider whether, in addition, they would consent to undergo synovial biopsy as part of a pilot study that will test the hypothesis that synovial tissue in RA patients carries a molecular and/or cellular signature ('pathotype') that can be captured to optimise the rational choice of biologic agents to thereby enhance the proportion of patients achieving high-hurdle endpoints.

Ultrasound-guided biopsy is a safe, well-tolerated technique that renders synovium accessible in a high proportion of patients. Following treatment with a variety of immune-modulatory agents, certain molecular and cellular features within synovial biopsies (e.g. SL-CD68 expression) predict subsequent clinical improvement. However, clinical trials and experience indicate heterogeneity of responses to targeting discrete cellular or molecular components of inflammation with biologic therapies such that at present, determining the optimum biologic therapy for a given individual is largely a matter of trial and error. Therefore we aim to investigate whether pathologic features within the synovial membrane (which we propose to call a 'synovial pathotype') could be used to direct the choice of biologic agent *a priori* and a sub-group of patients enrolling in the trial will be asked to undergo synovial biopsy. Specifically, we will address the question: does the use of rituximab in patients with synovial biopsies containing features commensurate with ectopic germinal formation, or of TNF blocker to patients with diffuse inflammation, improve the response rates? If successful, this study will provide a novel biopsy-led rationale for the choice of biologic agent. In addition, samples of serum, RNA and genomic DNA from all patients enrolled in ORBIT will contribute to the MRC-funded PEAC (Pathobiology of Early Arthritis Cohort) biobank. They will provide a resource for future analysis and separate relevant applications.

STUDY OBJECTIVES

Primary objectives:

- To compare the safety and efficacy of anti-TNF therapy and rituximab therapy in patients with active rheumatoid arthritis that meet the eligibility criteria for anti-TNF therapy according to the BSR/NICE guidelines.
- To compare the direct NHS costs associated with the care of RA patients treated with anti-TNF therapy and rituximab therapy.
- To estimate the incremental cost effectiveness ratio (ICER) of the more effective drug(s), if it is associated with higher costs; or the total NHS savings associated with prescribing the cheaper drug(s) if it is at least as effective as the more expensive drug.

Secondary objectives:

- To prospectively evaluate the influence of mood on both response to and side effect profile from anti-TNF and Rituximab.
- to identify whether synovial immuno-histology at baseline predicts differential response to rituximab and anti-TNF therapy.

STUDY DESIGN

This study will be an open label randomised controlled trial comparing two strategies of biologic therapy in biologic naïve patients over 12 months. The first treatment strategy will use rituximab first in the treatment sequence, followed by anti-TNF therapy in patients who stop rituximab because of inefficacy or toxicity. The second strategy will use the reverse sequence, starting with anti-TNF therapy before rituximab. Patients will not be withdrawn from the study if they do not respond to, or are intolerant of either treatment but will switch to the alternative (if clinically indicated). The purpose of this study is to compare, in terms of safety, efficacy and cost-effectiveness, the decision to begin treatment with rituximab or with anti-TNF therapy. The following protocols have been developed to clearly define these two treatment strategies, including the conditions under which it is advised that the current course of treatment should be considered unsuccessful, and the patient should be switched to the alternative therapy. However, at all times during the course of the study, the final decision as to

what treatment is to be given will reside with the patient and physician; this study aims to capture the variety of clinical pathways that different patients will follow and measure their outcomes, relating these back to the original (randomised) treatment strategy.

Patients will be assessed for inclusion at a screening visit to confirm eligibility. A trial patient information sheet and Arthritis & Rheumatism Campaign patient drug information leaflets about all biologic drugs will be provided to the patient. Patients will have a minimum of 48 hours to consider the information before written informed consent is obtained. Patients will be screened for Hepatitis B (with surface antigen and core antibody testing), Hepatitis C and latent TB infection (with CXR, tuberculin skin testing and T-SPOT according to the local protocol). Baseline data will be collected at a subsequent visit, followed by assessment at 12 subsequent monthly visits. Data will be collected as shown in the Study Flow Chart.

TREATMENT PROTOCOLS

Patients will be randomised via IVRS (organised through the Robertson Centre for Biostatistics, University of Glasgow) to receive rituximab or anti-TNF therapy. Minimisation will be applied to ensure similar numbers of patients are randomised to both groups who are intolerant of methotrexate, and (in those patients undergoing biopsy) who have diffuse inflammation or ectopic germinal centres on histology.

i. Rituximab therapy

Patients randomised to receive rituximab therapy will be given treatment as follows:

Day 1 and Day 15
- paracetamol 1g p.o. (30 minutes before rituximab)
- chlorpheniramine 10mg I.V. (30 minutes before rituximab)
- methyl prednisolone 100mg I.V. (30 minutes before rituximab)
- rituximab 1g by IV infusion

All treatment infusions will be prepared, administered and monitored according to the guidance included in the SmPC and in accordance with standard local practice. The paracetamol, chlorpheniramine and methyl prednisolone will be sourced locally.

Response to each course of rituximab will be assessed after three months and monthly thereafter until any subsequent course of rituximab; the categories of response are defined in table 1:

Non-responders – patients will be designated non-responders if their DAS28 has not improved by > 1.2 from baseline three months after each pulse of rituximab; patients will not be re-treated with rituximab and will be switched to anti-TNF therapy. At the discretion of the patient's rheumatologist, a patient may be designated a non-responder if their DAS28 has improved by >1.2, but their DAS28 remains above 5.1.

Partial responders – patients will be designated partial responders if their DAS28 improves by >1.2 from baseline but remains >3.2.

Good responders – patients will be designated good responders if their DAS28 falls by >1.2 to a level <3.2 (i.e. into a 'low disease activity state' [LDAS])

Remission – patients will be designated as in remission if their DAS28 falls to <2.6.

Toxicity – patients with drug-related toxicity (as defined by the treating rheumatologist) will be switched to anti-TNF therapy if/when the investigator deems it safe and appropriate.

Up to three courses (a course is defined as two x 1g infusions) of rituximab therapy may be given within a 12 month period in patients who are responding to therapy. The indications for re-treatment are as follows:

'Treat-to-target' – the treatment strategy is designed to achieve LDAS. To this end, patients will be re-treated every 6 months if their DAS28 remains above 3.2, six months after each course of treatment.

Patients in LDAS will have their treatment deferred until such time as their DAS28 rises above 3.2.

e.g., a patient with baseline DAS28 of 6.0 who improves to a DAS28 of 4.5 after 6 months would be re-treated after 6 months

e.g. a patient with baseline DAS28 of 6.0 who improves to 3.0 after 6 months would not be re-treated; however, if their DAS28 rises to 3.3 after seven months they would then be re-treated

Flare – a flare is defined as a rise in DAS28 of >1.2 between monthly assessments. Patients who flare may be re-treated provided that a minimum of 20 weeks has elapsed from their previous treatment;

e.g., a patient with baseline DAS28 of 6.0 who improves to a DAS28 of 3.2 after 3 months but whose disease flares, with a rise in DAS28 to 4.5 after 4 months, would be re-treated after 20 weeks.

ii. Anti-TNF therapy

Patients randomised to 'anti-TNF' therapy will be prescribed either adalimumab or etanercept following discussion between the patient and their rheumatologist. The following dosages will be prescribed:

Etanercept	50mg/week, by sub-cutaneous injection
Adalimumab	40mg every other week by sub-cutaneous injection. In patients not receiving MTX this may be increased up to a maximum of 40mg/week if necessary.

All injections will be administered and monitored according to the guidance included in the SmPC for each product. All drugs will be administered according to standard local practice, usually by the patient/carer at home after appropriate training.

Initial response to therapy will be assessed after 3 months and every month thereafter using the same criteria as for rituximab:

Non-responders – patients will be designated non-responders if their DAS28 has not improved by > 1.2 from baseline (primary non-response) or returns to a value within 1.2 of their baseline level (secondary non-response); treatment will be stopped and the patient will be switched to rituximab. At the discretion of the patient's rheumatologist, a patient may be designated a non-responder if their DAS28 has improved by >1.2, but their DAS28 remains above 5.1.

Partial responders – patients will be designated partial responders if their DAS28 improves by >1.2 from baseline but remains >3.2.

Good responders – patients will be designated good responders if their DAS28 falls by >1.2 to a level <3.2 (i.e. to a LDAS).

Remission – patients will be designated as in remission if their DAS28 falls to <2.6.

Toxicity – patients with drug-related toxicity will be switched to rituximab if/when the investigator deems it safe and appropriate.

Table 1 – categories of response

DAS28 improvement from baseline	Post-treatment DAS28	Category of response
< 1.2	Any	Non-responder. Switch to alternative.
> 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

Treatment strategies

Patients who fail to respond, lose response, or stop their assigned therapy because of adverse events will be switched to the alternative technology. Patients who fail both treatment modalities will be continue to be treated by their attending rheumatologist with appropriate DMARD therapy and will continue to be followed up (unless consent is withdrawn). Deviations from the usual treatment schedules (for example, because of intercurrent infection) will be recorded but will not necessitate withdrawal from the trial. Analysis will be performed by intention to treat, and so the trial will effectively compare two treatment strategies – anti-TNF first or rituximab first in the treatment sequence.

Outcome measures

The primary outcome measure will be the mean change in DAS28 between 0 and 12 months

The secondary outcome measures will include:

- area under the curve (AUC) of mean improvement in DAS28 over time between 0 and 12 months
- incremental cost effectiveness of each strategy – this will be estimated using the average direct NHS costs per utility gain over 12 months.
- percentage of patients with low disease activity (DAS28 < 3.2) at 3, 6, 9 and 12 months
- percentage of patients in remission (DAS28 < 2.6) at 6 and 12 months
- ACR20, 50 and 70 response rates at 6 and 12 months
- mean % change in DAS28 between 0 and 12 months
- mean change in HAQ score between 0 and 12 months
- effect of depression on response and side effect profile
- serious adverse events over 12 months; the rate of serious adverse events in the six month period following a switch from one technology to the other will be compared
- the effect of synovial immuno-histology on drug response rates

Sample size and power calculations

The study is powered to demonstrate equivalence between the two treatment strategies in the change from baseline DAS28 score after 12 months of treatment. If the true treatment effect difference is zero, and assuming a standard deviation of 1.6 units for the change in DAS28 after 12 months (based on the REFLEX Study, a Phase 3 study conducted by Roche, comparing rituximab plus methotrexate with methotrexate alone), then a study of 151 patients per group would have 90% power to demonstrate equivalence between the study groups within equivalence limits of 0.6 units (the measurement error of DAS28). Note that this sample size would also have 90% power to show equivalence within a limit of 1.2 units (the minimum clinically significant difference in DAS28) if the true treatment effect difference is as large as 0.6 units.

STUDY POPULATION

Inclusion criteria

Patients with RA who meets the BSR guidelines for anti-TNF therapy and who:

- fulfil the 1987 criteria of the ACR classification criteria for a diagnosis of RA
- have failed standard therapy, as defined by a failure to respond or tolerate adequate therapeutic trials of at least 2 standard DMARDs, one of which must have been methotrexate
- have not previously been treated with biologic therapy
- have active disease, as measured by the modified disease activity score, and as defined in the current BSR guidelines
- are sero-positive for rheumatoid factor or anti-CCP antibodies
- age > 18 years of age

Exclusion criteria

Patients will be excluded if they have any contraindication to anti-TNF therapy or rituximab therapy:

- women who are pregnant or breast-feeding
- 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.
- history of or current inflammatory joint disease or autoimmune disease other than RA
- treatment with any investigational agent ≤ 4 weeks prior to baseline or < 5 half-lives of the investigational drug
- intra-articular or parenteral corticosteroids ≤ 2 weeks prior to baseline.
- active infection
- septic arthritis within a native joint within the last 12 months
- sepsis of a prosthetic joint within 12 months or indefinitely if the joint remains in situ
- known HIV or hepatitis B/C infection
- latent TB infection unless they have completed adequate antibiotic prophylaxis
- malignancy (other than basal cell carcinoma) within the last 10 years
- New York Heart Association (NYHA) grade 3 or 4 congestive cardiac failure
- demyelinating disease
- latex allergy or allergy to excipients in any of the study medications
- any other contra-indication to the study medications as detailed in their summaries of product characteristics

Acceptable forms of effective contraception include:

- established use of oral, injected or implanted hormonal methods of contraception
- placement of an intrauterine device (IUD) or intrauterine system (IUS).
- barrier methods of contraception: Condom or Occlusive cap (diaphragm or
- cervical/vault caps) with spermicidal foam/gel/film/cream/suppository
- male sterilisation (with the appropriate post-vasectomy documentation of the absence of sperm in the ejaculate)
- true abstinence: when this is in line with the preferred and usual lifestyle of the subject

Concomitant medications

Patients may be treated with non-steroidal anti-inflammatory drugs, analgesics and conventional DMARDs. Changes in concomitant medication and their doses are allowed and will be recorded. Oral corticosteroids may be prescribed at a dose not exceeding prednisolone 10mg/day (or equivalent), but the dose must remain stable throughout the trial. Intra-articular and intra-muscular triamcinolone may be used, but not within four weeks of the 6 and 12 month assessments. Live vaccines must not be given during the trial.

Screening

The interval between screening and baseline should not exceed 3 months.

Screening for latent TB infection

Patients should be screened for the presence of latent TB infection in accordance with local practice, comprising clinical history and examination, CXR, skin testing and T-SPOT testing, as appropriate.

Screening for Hepatitis

Patients should be screened for Hepatitis C and Hepatitis B (with both Hepatitis B surface antigen and Hepatitis B core antibody).

Synovial biopsy and biobank

The PEAC Biomedical Resource will be based at the Human Tissue Resource Centre (HTRC) and the Barts and The London Genome Centre (BLGC). These structures are core facilities provided by Barts and The London NHS Trust and School of Medicine with a track record in managing large biomedical and database resources including the MRC BRIGHT Study, NESTEGG, GAINS and Genetics of Sepsis and Septic Shock (GENOSEPT) studies. The teams managing these core facilities have considerable experience in overseeing: governance, ethics, compliance, audit and the application of uniform management and usage policies in accordance with data protection legislation and Human Tissue Act 2004. The curator of the PEAC Biomedical Resource will be Prof. C. Pitzalis (Coordinator of the PEAC Consortium) assisted by the PEAC Steering Committee and Scientific Advisory Board. All patients will have

blood samples taken and stored for metabolomics, RNA, serum, buffy coat, plasma and peripheral blood mononuclear cells. 50 patients will be asked to provide an additional 30mls of blood for epigenetic and biomarker analysis. Patients who agree to participate in the trial, and who attend a rheumatology unit with the facilities for ultrasound-guided per-cutaneous needle biopsy will be asked to consider synovial biopsy. All biopsies will be analysed by the PEAC central laboratory. The details of sample collection, handling, transfer and storage for the biobank are contained in the PEAC Central Laboratory Sampling manual.

Synovial biopsies will be analysed and classified as showing 'diffuse inflammation' or 'ectopic germinal centres' within seven days. The results will be used in the randomisation process (as above).

Informed Consent

Patients who are found to be eligible for the trial will be given verbal and written information about the trial and will be given a minimum of 48 hours to consider their potential involvement. Written, informed consent will be obtained from all patients who agree to participate in the trial. Patients who are asked to undergo synovial biopsy will be given a second patient information sheet, and if they agree to participate, will sign a second consent form. Patients who decide not to undergo synovial biopsy will still be eligible for the main study.

Withdrawal Criteria

Patients who fail to respond, lose response, or stop their assigned therapy because of adverse events will be switched to the alternative technology. Deviations from the usual treatment schedules (for example, because of intercurrent infection) will be recorded but will not necessitate withdrawal from the trial. Analysis will be performed by intention to treat, and so the trial will effectively compare two treatment strategies – anti-TNF first or rituximab first in the treatment sequence. Any patient who fails both therapies will be treated as appropriate by their attending rheumatologist, will continue to be followed up and will be analysed by ITT. Patients will be free to withdraw their consent at any stage. The study will be considered to be complete following the last study visit of the last patient.

DATA COLLECTION

All assessments will be performed by a nurse metrologist who will collect data as follows:

- demographic data including age, gender
- diagnostic information including the 1987 criteria of the ACR classification criteria for a diagnosis of RA, titre of rheumatoid factor and disease duration
- disease activity including ACR/EULAR core set, DAS28
- physical function using the Health Assessment Questionnaire
- health related quality of life and utility using EQ-5D.
- psychological state using Hospital Anxiety and Depression Scale
- drug therapy
- adverse events
- employment and number of days of sick leave
- direct NHS costs (investigations, routine blood monitoring, community and outpatient appointments, and inpatient stays)
- compliance

Assessment schedule –

- patients will have disease activity, therapy and adverse events assessed and recorded at baseline and monthly thereafter for 12 months.
- physical function, psychological state and health-related quality of life will be assessed at 0, 3, 6, 9 and 12 months.
- direct NHS costs will be assessed at 0, 6 and 12 months

Data will be entered on an eCRF developed by the Robertson Centre for Biostatistics, University of Glasgow. who will also co-ordinate data validation checks and query resolution.

MEDICATIONS

Investigational Product Descriptions

The investigational medicinal product used in the clinical trial is rituximab. This product has been approved with the European Commission decision (MA number: EU/1/98/067/002). The license holder of Mabthera® is Roche.

Product	Supplied as
Rituximab	50-mL vials with a solution concentration of 10mg/mL

Roche will provide sufficient study-specific supplies of rituximab for use in the study. Supplies of rituximab must be stored within a refrigerator at 2-8oC in a secure location in their original packaging in order to protect from light. Supplies of rituximab will be labelled with a computer generated label containing the appropriate information to meet regulatory requirements. Storage and supply of the rituximab will be delegated to the local pharmacy. Rituximab will only be released to sites once all the appropriate regulatory and governance approvals are in place. Pharmacy will supply the investigational medicinal product at each visit where rituximab is administered.

Comparator investigational medicinal products

Comparator investigational medicinal products in this clinical trial are etanercept and adalimumab. Local practice for prescribing and supply should be used for this clinical trial. No additional labelling will be applied.

Drug Accountability

A record of all study drug movements will be kept for accountability purposes. When rituximab is received by pharmacy, they will verify that drug supplies have been received intact, in the correct quantities and at the appropriate temperature. Drug accountability records for all used and unused supplies will include:

- An accurate running inventory at the site
- An individual subject study accountability log
- Return and disposal

They should include dates, quantities, batch numbers and expiry dates. Only those supplies intended for use in the study should be dispensed to study participants. These records should be maintained which adequately document that patients were provided with the doses specified in the protocol and that all study drug provided was fully reconciled. Logs will be provided to record drug accountability. These inventories must be made available for inspection by the study sponsor or their designee and regulatory agency inspectors.

Compliance

An assessment of compliance with study medication will be made at each study visit.

STATISTICAL ANALYSIS

Statistical analysis will be performed by the Robertson Institute of Biostatistics, University of Glasgow.

Study endpoints will be summarised by treatment group at each time point – that is, the primary analysis will compare the strategy of treating with anti-TNF first (before rituximab in the treatment sequence), versus the alternative strategy of using rituximab first. The primary analysis will be to compare the primary endpoint between study groups, using a linear regression model with adjustment for baseline DAS28, study centre and other variables used to stratify the randomisation. Linear regression models, with adjustment for stratification variables and baseline values as appropriate, will also be used to compare study groups with respect to secondary and exploratory outcomes. Logistic regression will be used for binary endpoints. Data transformations and bootstrapping methods will be considered for the analysis of continuous endpoints that do not meet distributional model assumptions.

MONITORING & EVALUATIONS

The first monitoring visit should take place within four weeks of notification that the first subject has been randomised at each centre. A further monitoring visit should take place within 12 months. At study closure, a final monitoring visit should be performed to ensure all outstanding actions have been addressed.

The minimum frequency of monitoring visits is as follows:

- Every six-twelve months for centres with 20 or more patients
- At least every twelve months for centres with fewer than 20 patients

Where visits are occurring less frequently than every six months, contact with the centre should be maintained by telephone or letter to ensure that any safety or GCP issues are captured.

ASSESSMENT AND REPORTING OF ADVERSE EVENTS/REACTIONS

Definitions:

Adverse Event (AE)
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.

Adverse Reaction (AR)
Any untoward and unintended response in a subject to an investigational medicinal product which is related to any dose administered to that subject.

Serious Adverse Event (SAE) or Serious Adverse Reaction (SAR)

Any adverse event or adverse reaction that
a. results in death
b. is life threatening
c. requires hospitalisation or prolongation of existing hospitalisation
d. results in persistent or significant disability or incapacity
e. consists of a congenital anomaly or birth defect.
f. is otherwise considered medically significant by the investigator
   i.e. important adverse events/ reactions that are not immediately life-threatening or do not result in death or hospitalisation but may jeopardise the subject or may require intervention to prevent one of the other outcomes listed above

Suspected Serious Adverse Reaction (SSAR)
Any adverse reaction that is classed in nature as serious and which is consistent with the information about the medicinal product in question set out in the summary of product characteristics (SmPC).

Suspected Unexpected Serious Adverse Reaction (SUSAR)
Any adverse reaction that is classed in nature as serious and which is not consistent with the information about the medicinal product in question set out in the summary of product characteristics (SmPC).

DETECTION, RECORDING, and REPORTING of ADVERSE EVENTS

Participants will be asked at each study visit about the occurrence of adverse events since the last visit.

All Adverse Events (AEs) will be recorded, notified, assessed, reported, analysed and managed in accordance with the Medicines for Human Use (Clinical Trials) Regulations 2004(as amended). Detailed guidance is provided in Glasgow CTU Standard Oprerating Procedures (SOPs)18.001, 18.002 and 18.003. These can be found on the Glasgow Clinical Trials Unit website www.glasgowctu.org.

Full details of all AEs including the nature of the event, start and stop dates, severity, relationship to study drug and outcome will be recorded in the subject's medical records and on the study electronic case record form. AEs will be monitored and followed up until satisfactory resolution or stabilization.

All adverse events must be assessed for **seriousness, causality, expectedness and severity**. This assessment will be undertaken by the Principal Investigator.

All Serious Adverse Events (SAEs) arising during the Clinical Trial will be reported to the sponsor by entering the details into the electronic case record form as soon as reasonably practicable and in any event within 24-48 hours of first becoming aware of the event. Any follow up information should also be reported.
The SAE details will be entered onto the Glasgow Clinical Trials Unit Pharmacovigilance database.

SAEs that occur at any time after the inclusion of the subject in the study (defined as the time when the subject signs the informed consent) up to 30 days after the subject completed or discontinued the study will be reported.

The subject is considered to have completed the study **either** after the completion of the last visit or contact (e.g., phone contact with the investigator or designee), **or** after the last dose of the study medication, whichever is later. The date of discontinuation is when a subject and/or investigator determine that the subject can no longer comply with the requirements for any further study visits or evaluations.

Suspected Unexpected Serious Adverse Reactions
Any AE that is assessed as **serious**, is suspected of having a **causal relationship** to the trial medication and is **unexpected** is a **Suspected Unexpected Serious Adverse Reaction (SUSAR)** and will be reported in an expedited manner to the MHRA and Research Ethics Committee.

Fatal or life threatening SUSARs: not later than 7 days after the sponsor had information that the case fulfilled the criteria for a fatal or life threatening SUSAR, and any follow up information within a further 8 days.

All other SUSARs: not later than 15 days after the sponsor had information that the case fulfilled the criteria for a SUSAR.

Principal Investigators at each site will be informed about any **SUSARs** which have occurred during the study.

Pregnancy

Pregnancy is not considered an AE or SAE. However, the PI will report **pregnancy** information on any female subject or female partner of a male subject who becomes pregnant while participating in the trial to the sponsor within two weeks of first becoming aware of the pregnancy. This report should be provided on the Pregnancy Notification Form provided by the sponsor (on www.glasgowctu.org).
The pregnancy should be followed up by the investigator until delivery. It may be necessary to monitor the development of the newborn for an appropriate period post delivery. Information on the status of the mother and child should then be reported to the sponsor. Any resulting Serious Adverse Event should be reported as per the procedure above.

ANNUAL SAFETY REPORTING

An annual safety report will be submitted to the MHRA and Research Ethics Committee as soon as is practicable after the anniversary of the issue of the Clinical Trials Authorisation. The Chief Investigator will submit this report on behalf of the sponsor in liaison with Glasgow Clinical Trials Unit Pharmacovigilance Office as per GCTU SOP 18.003.

DATA MONITORING COMMITTEE

A Data Monitoring Committee will review summary safety information and oversee the safety of the participants in the trial.

INDEMNITY AND INSURANCE

NHS employed researchers will be covered for negligent harm through the NHS Clinical Negligence and Other Risks Indemnity Scheme (CNORIS).

FUNDING

The study is being funded by an educational grant from the Arthritis & Rheumatism Campaign. Rituximab is being provided free of charge by Roche Pharmaceuticals Ltd.

PUBLICATION AND ARCHIVING

It is anticipated that the results will be published in a peer reviewed journal. Any investigator involved with this study is obligated to provide the Sponsor with complete test results and all data derived from the study on request. Data will be stored and archived by the Robertson Centre for Biostatistics, University of Glasgow for a minimum of five years.

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