NETSCC, HTA

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TACIT

Tumour-necrosis-factor inhibitors against combination intensive therapy.

TRIAL PROTOCOL

1 Trial Identifier

1.1. Full Title of Trial
Randomised controlled trial of tumour-necrosis-factor inhibitors against combination intensive therapy with conventional disease modifying anti-rheumatic drugs in established rheumatoid arthritis

1.2. Acronym
The TACIT trial

1.3. Short Title
Tumour-necrosis-factor inhibitors against combination intensive therapy

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1.8. Sponsor
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2 Background Information

2.1. Rheumatoid Arthritis
Rheumatoid arthritis (RA) is the commonest disabling UK disease, affecting 1% of adults. Disability is due to persisting joint inflammation, progressive joint damage and extra-articular features. RA reduces life expectancy due to co-morbidities like coronary artery disease[1]. There are substantial costs from medical and social care and employment loss. One systematic review, pre-dating "biologic" therapies, showed costs were £55-£70M per million population (£4 billion for the UK)[2].

The aim of therapy is to reduce disease activity and erosive damage thus reducing disability[3]; cheap, readily available DMARDs like methotrexate go a long way towards this. Combination DMARDs are often more effective than monotherapy, without a major increase in toxicity, but UK rheumatologists have been slow to adopt this practice. Many patients go straight from DMARD monotherapy to TNF-inhibition; currently NICE does not require an intervening period of combination therapy. The central question in our proposed clinical trial is to find the right clinical and economic balance between combination DMARDs and TNF inhibition in active established RA patients who have failed two DMARDs.

2.2. Drugs and Biologics Used in the Treatment of RA

Conventional DMARDs: Those in routine use include methotrexate, sulfasalazine, leflunomide, hydroxychloroquine and ciclosporin. Methotrexate is the most widely used and is now considered a benchmark against which new agents must be tested; it is a component of almost all combination drug and biologic regimes used in early and established RA.

DMARD combinations were initially advocated by McCarthy[4]. Since initial RCTs evaluated combinations with excessive toxicity (gold-hydroxychloroquine)[5] or limited efficacy (methotrexate-azathioprine)[6], early reviews suggested risk/benefit ratios were unfavourable compared to monotherapy[7]. The situation changed when RCTs of methotrexate-ciclosporin[8], methotrexate-sulfasalazine-hydroxychloroquine[9] and methotrexate-sulfasalazine-steroids[10] reported improved disease control with mild excess toxicity in active RA; similar results were obtained in subsequent combination therapy studies. Combination DMARDs are not required for all RA patients; they did not add benefit in patients with mild established RA who were stable on DMARD monotherapy[11]. Overall, from our 2005 systematic review[12] and as suggested by a gradual expansion of its use in routine practice, the benefits of combination therapy are thought to outweigh the risks in patients with active disease poorly-controlled by monotherapy such as those being considered for anti-TNF treatment.

Steroids In established RA, steroids (intra-articular, intra-muscular or oral) are mainly used as adjunctive therapy in managing disease flares. In early disease it has been suggested that they exert a disease-modifying effect and they form an initial but temporary component of several early arthritis combination regimes.

TNF-inhibitors in RA: These agents were developed in the late 1980s to target TNF-α, a cytokine of central importance in the pathogenesis of RA, which exerts its effects by binding to Type 1 (p55) and Type 2 (p75) receptors on immune, inflammatory and endothelial cells. Three agents are approved for RA and all are similarly effective.

- *Infliximab* is a chimeric (human-murine) IgG1 antibody given intravenously. It binds to soluble and membrane-bound TNF-α with high affinity blocking TNF-α-receptor interactions; unlike other agents, it is cytotoxic for TNF-bearing cells.
- *Etanercept* is a recombinant soluble p75 TNF-receptor-Fc fusion protein given subcutaneously. It is a dimer of covalently bound high affinity type 2 (p75) TNF receptors linked to the Fc portion of human IgG1. Etanercept binds to TNF-α, preventing it from interacting with its receptor; unlike the other two agents it also targets TNF-β (lymphotoxin).
- *Adalimumab* is a recombinant humanised monoclonal anti-TNF-α antibody given subcutaneously. It binds to human TNF-α with high affinity and, as a consequence, stops the cytokine binding to its receptors.

Infliximab must be given concurrently with methotrexate (or another DMARD in methotrexate intolerant patients) to prevent the formation of human anti-chimeric antibodies. The licence for adalimumab also requires concomitant methotrexate unless the patient is intolerant. Though concomitant treatment is not required for etanercept, substantial data suggests combination treatment is more effective. Therefore all three drugs are almost always given with methotrexate or another DMARD.

2.3. Current Access to TNF Inhibitors

International groups[13], specialist societies[14,15] and regulatory bodies[16] recommend TNF inhibitors for patients with active RA who fail conventional DMARDs. Views differ on what constitutes active RA[17]; the UK uses a disease activity score (DAS) over 5.1. The concept of "failing DMARDs" is also controversial. In 2001 NICE accepted the advice of the British Society for Rheumatology (BSR) that TNF-inhibitors should be available in the UK for patients with active RA who failed “to respond to or tolerate adequate therapeutic trials of at least 2 standard DMARDs" including methotrexate. These criteria, which are based on consensus expert opinion[14], have not subsequently changed. Despite such UK restrictions, the high cost of TNF inhibitors (£10,000/case/year) creates a large and increasing NHS financial burden. By 2005, the UK BSR Biologics Register had registered nearly 10,000 RA patients on TNF inhibitors costing

nearly £100M/year. As new cases meet the eligibility criteria annually and most patients require long-term therapy, TNF-inhibitor use may rise 2-3 fold in the next decade, costing over £300M/year (2006 prices). Technical reasons make low cost generic biologics unlikely. Costs will also increase when further biologics are introduced initially for anti-TNF non-responders; two new expensive agents licensed in the USA are rituximab (anti-B cell therapy)[18] and abatacept (T-cell activation modulator)[19].

An alternative strategy for the use of biologics in RA is crucial to assist NICE[16] in best balancing the wishes of patients and doctors for easy access to effective therapies against the pressure to restrict high cost agents to those most in need. The strategy must be based on good scientific evidence, be transparent and equitable and consider patients' views. This is crucial as many patients and rheumatologists remain worried that even current NICE guidance is denying the best treatment to some patients and a recent national survey supports these concerns. Our proposed trial would be a first step in this process.

2.4. Alternative Strategy for TNF-Inhibitors

We propose, based on our systematic review that TNF-inhibitors are given in RA only if intensive DMARD combination treatment has failed. Placing TNF-inhibitors lower down the therapeutic cascade will be more cost-effective for the NHS and better serve the interests of RA patients for three reasons:

a) *Inequity of Access:* At present, many patients do not get the rapid access to TNF inhibitors intended by NICE guidance at least in part for financial reasons; this problem is likely to become worse.
b) *Treatment Risks:* TNF-inhibitors have known serious risks (such as a substantial increase in infections and a likely increase in cancer, particularly lymphoma, risk); their long term safety profile is unknown. Combination DMARDs also have side effects but, by and large these are not irreversible and are well-defined.
c) *Lack of Response:* TNF inhibitors are not universally effective in RA with a response failure rate of over 30%; some of these patients may have responded to the much less expensive combination DMARD regimes

Importantly, we do not anticipate our study will lead to those RA patients who need TNF inhibitors being denied them but to more cost-effective use of these agents. If our study suggests combination DMARDs are equally effective for at least some RA patients, those for whom there is no alternative will receive the high-cost biologics earlier and more reliably than they do now.

2.5. Systematic Review Comparing TNF Inhibitors and Intensive DMARD Combinations

Method: We undertook a systematic review comparing the efficacy of TNF-inhibitors (used with methotrexate or another DMARD as in routine practice) with combination therapy using two or more conventional DMARDs. We included RCTs in English of at least 6 months duration using agents licensed for routine practice. In each study at least one treatment arm involved either combination DMARDs or TNF-inhibitors; another arm involved DMARD monotherapy. We excluded combinations not allowed in our RCT because of excessive toxicity (gold with anti-malarials or ciclosporin; combinations with pencillamine or cyclophosphamide) or inefficacy (combinations with azathioprine). Methotrexate-sulfasalazine was originally omitted for inefficacy since RCTs available in established RA either showed no benefit[20,21] or found methotrexate-sulfasalazine-hydroxychloroquine more effective[9,22]. However, a very recent RCT in press[23] in early RA shows some benefit by DAS but not ACR response criteria; the combination will thus be allowed but only for those intolerant to other drugs.

We divided the RCTs identified into early RA (≤24 months RA, no prior DMARDs) and, of more relevance to our study, established RA (≥over 12 months duration, ≥one prior DMARD). Within the systematic review, we undertook a meta-analysis, using standard software (Review Manager

4.2.8), which included all trials using ACR-50 and ACR-70 as outcomes (≥50% or 70% improvement respectively in ACR core set of 7 clinical and laboratory measures)[24]. ACR-50 was selected as the critical measure as it represents the lowest level of meaningful clinical change[25] (most appropriate for high cost therapy) as opposed to ACR-20 which represents the smallest detectable changes.

Early RA: The BeSt trial[26] is the only head to head RCT comparing TNF inhibition directly with combination DMARDs. 508 patients received intensive combination DMARDs plus steroids or TNF inhibitor (infliximab) plus methotrexate or DMARD monotherapy. ACR-20 responses were identical in both groups (79%). However, on TNF inhibitors, 40% achieved ACR-70 responses and 81% remission whilst, on combination DMARDs, only 28% achieved ACR-70 and 73% remission. Thus TNF inhibitors may appear better with stringent measures like ACR-70 or remission but not with less rigorous measures like ACR-20; sadly ACR-50 was not reported so we cannot assess disparity in lowest meaningful clinical change.

There were 9 other RCTs versus DMARD monotherapy, 2 with TNF inhibitors[27,28] and 7 with intensive DMARD regimens[10,29-35]. A meta-analysis including BeSt[26] (see Table) shows combination DMARDs may be slightly better for ACR-50.

Meta-analysis of RCTs in Early RA Involving TNF Inhibitors and Combination DMARDs
All trials reporting the relevant outcome measures
Effect size given as odds ratio (95% confidence intervals)

Outcome	TNF-inhibitors plus methotrexate			Combination DMARD		
	RCTs	*Patients*	*Effect size*	*RCTs*	*Patients*	*Effect size*
ACR-50	2	1166	1.86 (1.47, 2.36)	8	958	2.94 (2.23, 3.87)
ACR-70	3	1420	2.13 (1.68, 2.68)	6	780	2.21 (1.57, 3.11)

Established RA: there were 12 RCTs, 5 involving TNF-inhibitors[36-40] and 7 involving combination DMARDs[8,9,22,41-]; all were against monotherapy and none involved a head to head comparison of TNF inhibitors with combination DMARDs. The table show results from a meta-analysis of these trials. DMARD combinations and TNF inhibitors produced comparable ACR-50 and ACR-70 responses; ACR-50 responses may be better with combination DMARDs.

Meta-analysis of RCTs in Established RA: TNF Inhibitors and Combination DMARDs
All trials reporting relevant outcome measure
Effect size given as odds ratio (95% confidence intervals)

Outcome	TNF-inhibitors plus methotrexate			Combination DMARD		
	RCTs	*Patients*	*Effect size*	*RCTs*	*Patients*	*Effect size*
ACR-50	5	1487	3.89 (3.02, 5.03)	6	720	5.79 (3.73, 9.00)
ACR-70	5	1487	4.06 (2.94, 5.62)	5	653	3.33 (1.95, 5.68)

Change in HAQ scores was reported in 8 RCTs in the established RA systematic review. The minimal clinically important HAQ change in RCTs is 0.22 although in routine practice individuals may only perceive larger changes (up to 0.31)[45]. The table shows mean HAQ changes in TNF inhibitor and combination DMARD studies. For TNF inhibitors, the difference in mean HAQ change compared to DMARD monotherapy was 0.2-0.4; for DMARD combinations it was 0.1-0.3. The clinical relevance of this is unclear as the methods used to report the variation in mean HAQ scores differ from study to study.

Mean changes in HAQ scores: RCTs of TNF inhibitors and DMARD combinations

TNF Inhibitors					DMARD Combinations				
		Cases	*HAQ Change*	*Diff*			*Cases*	*HAQ Change*	*Diff*
Klareskog	Methotrexate	228	0.6	0.4	Tugwell	Methotrexate	73	0	0.3
	Methotrexate-Etanercept	231	1.0			Methotrexate-Ciclosporin	75	0.3	
Weinblatt, Kremer	Methotrexate	30	0.4	0.3	*Kremer*	Methotrexate	133	0.1	0.3
	Methotrexate-Etanercept	59	0.7			Methotrexate-Leflunomide	130	0.4	
Lipsky	Methotrexate	88	0.3	0.2	*Dougados*	Leflunomide	50	0	0.1
	Methotrexate-Remicade	86	0.5			Leflunomide-Sulfasalazine	56	0.1	
Weinblatt, Keystone	Methotrexate	62	0.3	0.3	*Lehman*	Methotrexate	27	0.4	0.1
	Methotrexate-Adalimumab	67	0.6			Methotrexate-Gold	38	0.5	

Erosive x-ray damage, a surrogate for ultimate disability, was also assessed in the TNF inhibitor studies included in the established RA review. Compared to DMARD monotherapy, TNF inhibitors substantially reduce damage as assessed by x-rays[46] and magnetic resonance imaging[47]. However, there is no comparable data in the DMARD combination studies.

2.6. Observational Studies of DMARD Combination and TNF Inhibitor Efficacy in RA

An observational study from Leeds[48] evaluated intensive DMARD therapy in RA patients who had failed conventional DMARD therapy. 308 such RA patients were treated by escalating their conventional therapy to include combination DMARDs and parenteral methotrexate. Out of 159 patients, who retrospectively met BSR/NICE biologics eligibility criteria, 93 responded to escalated DMARDs; 21% showed good response (by European criteria[49]) at 6 months and 7% achieved remission or near remission. A recent report from the BSR biologics register[50] described similar responses in 3223 UK RA patients given etanercept or infliximab; at 6 months 18% had good responses and 9% had achieved remission.

2.7. Serious Adverse Effects of Combination DMARDs and TNF Inhibitors

This analysis focuses primarily on serious adverse events that are likely to lead to long term toxicity or death.

DMARDs: bone marrow, liver and lung toxicities are the main concerns. Monitoring with regular blood tests based on national guidelines minimises bone marrow and liver risks; an observational study of 2,747 patients showed methotrexate had comparable toxicity to non-steroidal anti-inflammatory drugs[51]. Recent practice changes have also minimized methotrexate lung disease[52]. Large cohort studies (>40,000 cases) show liver and lung toxicity is rare with new DMARDs like leflunomide[53-55]. Immunosuppressive DMARDs like methotrexate have been felt to raise cancer (especially lymphoma) risk, over and above the increase seen in untreated severe RA[56]; however the most recent study by Wolfe and Michaud [57] suggests a small non-significant increase (standardised incidence ratio for methotrexate 1.5, 95% CI 0.8-2.7; for untreated RA 1.3, 95%CI 0.5-3.1).

Systematic reviews of DMARD combinations show some increase in toxicity over monotherapy. The early review by Felson concluded risks exceeded benefits[7] but recent reviews suggest the balance favours DMARD combinations[12,58-60]. One reason is that currently used combinations are less toxic; another is greater experience using DMARDs alone or in combination[61-65].

TNF-Inhibitors: Serious infections are a major concern[66-68], including reactivation of prior tuberculosis[69,70] (number needed to harm 59 patients). Cancer risks are the other main concern.

They were highlighted in the only systematic review of toxicities in RCTs of TNF inhibitors[68]; it evaluated infliximab and adalimumab but not etanercept and reported a dose-related increased solid and haematogenous cancer risk (number needed to harm 154 patients). So far national registries have not identified an increase in solid cancers[71,72] but all studies report more lymphomas in patients on TNF inhibitors[57,68,74]. As with DMARDs, the pre-existing association of lymphomas with severe RA and systemic inflammation makes assessing the exact contribution of TNF inhibitors complex; however, Wolfe and Michaud[57] show a significant increase with a standardised incidence ratio of 2.9 (95% CI 1.7-4.9) with these drugs compared to 1.5 for methotrexate and 1.3 for untreated RA.

Mortality: DMARD monotherapy, particularly methotrexate, reduces RA mortality[75]. There is limited data on deaths with DMARD combinations, but a long-term Scandinavian study found no treatment-associated deaths with intensive therapy including DMARD combinations[76]. There is limited published data on deaths with TNF-inhibitors, but there are anecdotal concerns; 3 UK units reported that 12 of the first 146 patients receiving TNF inhibitors developed serious infections and 4 died[77]. At Kings College Hospital we have had 2 treatment-related deaths in the first 90 cases treated with TNF inhibitors.

2.8. Adjunctive Steroid Efficacy and Toxicity

Efficacy: A systematic search identified 12 RCTs in which steroids were given with DMARDs in active RA[78-89]. Some RCTs of early RA treatment strategies include short-term steroids. These RCTs are heterogeneous and cannot be combined in a single meta-analysis. However, the evidence suggests that in the short-term - a few weeks to a few months – steroids are effective in reducing symptoms, but in the long-term their benefits are limited and there is excess toxicity. Our own unit[79] reported falls in DAS of 0.6 over 6 months with intermittent IM depomedrone but changes were not sustained. Thus low-dose steroids are a useful bridging therapy when initiating intensive DMARD combinations, but have limited long term value.

Toxicity: The long-term risks of systemic steroids are well known and include infections, hypertension and osteoporosis. The overall value of steroids in RA is controversial. Some experts believe benefits outweigh risks[90]; others are more sceptical[91]. Our view, based on our 2-year RCT[79], is that the long-term risks outweigh the benefits, a view confirmed in another recent RCT[78]. However, when steroids are used for short-term flare management their benefits outweigh the risks[92].

2.9. Health Economic Issues

Costs of RA: there are substantial direct and indirect costs[2,93] particularly in patients with high HAQ scores[94,95]. Studies have also measured costs per quality adjusted life year (QALY) using the EuroQuol (EQ)5D[96,97] (despite its limitations in RA[98]), and converting HAQ scores.

Evaluation of TNF-inhibitors And Intensive Combination Therapy with DMARDs: a systematic literature search identified 17 papers on costs and cost-effectiveness of TNF inhibitors in RA[99-116]. An early analysis by Choi and colleagues[103] concluded that if 15 mg/week MTX is considered cost-effective for achieving ACR-70 responses in MTX-naive RA patients, then triple therapy is equally cost-effective in MTX-resistant RA. Whether etanercept and MTX combinations are considered cost-effective depends on whether $34,800/ACR-70 is considered acceptable. The current additional costs of giving TNF inhibitors in the UK over and above standard care is about £10,000/year for each patient remaining on therapy. The overall economic benefits of TNF inhibition are controversial. Publications generated by collaboration with the manufacturers suggest TNF inhibition is cost-effective by the common threshold of £30,000 per quality-adjusted life-year (QALY)[102,107-109]. Reports commissioned by regulators and those using independent data suggest substantially less cost-effectiveness.[101,116]. Much of these differences can be explained by the choice of economic model used and the key assumptions made[105]; at present there is no definitive answer about the overall cost-effectiveness of TNF-inhibitors. Analysis of two early RA trials of combination therapy with conventional DMARDs

showed combined treatment is cost-effective due to enhanced efficacy at lower or equal direct costs[117] and it reduces work-disability, which is a good indicator of overall costs[118]. There is little data on the cost-effectiveness of intensive combination therapy with DMARDs in established active RA; interestingly we have shown it is not cost-effective to give intensive combination DMARDs in stable, inactive established RA[11].

2.10. Conclusions

Irrespective of the overall benefits of TNF inhibitors in RA we consider the similarity of responses with intensive combination DMARDs in the only head to head RCT, the comparability of responses to both forms of treatment in DMARD monotherapy controlled RCTs (in early and late RA) and in observational studies provide clear-cut scientific justification for our proposed trial.

3 Trial Objective and Purpose

TNF inhibitors are a major innovation in treating rheumatoid arthritis (RA). However, they are not curative so best practice needs continual review[119]. NICE (National Institute for Clinical Excellence) states they should be available to active RA patients who have failed two disease modifying anti-rheumatic drugs (DMARDs); these criteria are consensus not evidence based. Our alternative view is that many such patients do equally well on intensive combination therapy with conventional DMARDs.

The objective of the proposed randomised controlled trial (RCT) is to test the hypothesis that active RA patients, who meet the NICE criteria for treatment with TNF inhibitors, will gain equivalent benefit from intensive combination therapy (two or more DMARDs and steroids) at substantially less expense and without increased toxicity. This hypothesis will be tested in a two arm pragmatic 12 month RCT using open-label treatments.

Key outcomes will be:

a. *Primary Outcome Measure*: Heath Assessment Questionnaire (HAQ), the key patient-completed disability measure in RA
b. *Secondary Outcome Measures*: joint damage, quality of life, disease activity, withdrawal rates, adverse effects
c. *Economic Evaluation*: societal costs, cost-effectiveness and cost-utility.

4 Trial Design

4.1. General

The proposed RCT will be an open-label, pragmatic, randomised, multicentre, two-arm trial comparing TNF inhibitors with combination DMARDs in active established RA. The duration of the trial will be 12 months. Patients who fail to respond in the combination therapy arm will be eligible for TNF-inhibitors at 6 months; this is the optimal period to judge responsiveness to DMARDs. Patients in the TNF inhibitor arm will be assessed for response to their first TNF inhibitor at 6 months reflecting NICE guidance; those who do not respond will try another TNF inhibitor for 6 months but if they fail they will need to receive alternative treatments like combination DMARDs.

The trial will be unblinded because individually optimised intensive DMARD therapy cannot be given blindly; previous RCTs in RA using such treatments were unblinded[11,26,30,33-35]. This approach will also provide the closest possible approximation to routine clinical care. One disadvantage of an unblinded study - that the clinicians will have excessive influence on the results - will be substantially ameliorated because the primary outcome measure, HAQ, and a key secondary outcome, SF-36, are patient self-completed questionnaires. In addition, another key outcome measure, x-ray changes will be read without knowledge of treatment group.

4.2. Target Population

The planned trial will be aimed at patients with RA presently attending outpatient rheumatology clinics in England and Wales who meet the current NICE criteria for receiving TNF inhibitors.

4.3. Clinical Outcome Assessments

Health Assessment Questionnaire, SF-36 and EQ5D: we will use the Health Assessment Questionnaire (HAQ), SF-36 and EQ5D to assess RA disability; these are all self-assessment questionnaires[120].

The standard approach in RA trials is to use disease-specific measures, particularly HAQ[121]. This is the dominant disease-specific instrument[122] for physical disability and assesses the capacity to perform a range of daily living and self-care activities. Scores range from 0 to 3, with higher scores indicating greater disability. It has established reliability and validity and has been used in over 100 published RCTs. An analysis of 1817 patients enrolled in 3 large recent DMARD RCTs in RA showed HAQ measures DMARD efficacy better than physician assessments like joint counts [123].

An additional approach is to use generic measures such as the *SF-36*[124]and EQ5D[125], which allow comparison with other diseases[126] but are relatively insensitive. SF-36 is the dominant generic assessment instrument[127]; it is widely used in RA RCT and has been shown to detect changes with DMARDs[128] and TNF inhibitors[129]. EQ5D has also been widely used in RA. Both the SF-36 and the EQ5D will be used to estimate quality-adjusted life years.

Erosive Damage. This is another key outcome, which acts as a surrogate for ultimate disability levels. It can be assessed using standard x-ray scoring systems[130] like the Larsen score[131] modified for minor changes[132] which we will use in our study.

Disease Activity. There are several methods of assessment. USA trials use ACR-20, 50 and 70 response criteria with most emphasis on ACR-50[25]. Disease Activity Scores (DAS) modified for 28 joint counts (DAS-28)[133] are the UK standard though variability causes concern[134]. Scores range from 1-10 based on changes in joint counts, patients' global assessments and ESR; high scores show active disease. In this trial ACR responses and DAS-28 will be collected; the DAS-28 scores will be used to determine appropriate pre-defined treatment targets.

Adverse Effects and Safety. The toxicity of TNF inhibitors and DMARD combinations are well known. The planned trial will follow national guidelines for their use, including regular safety monitoring[14,135]. Adverse events will be collected by patient reporting and recording of specific events (like hospital admission) following international guidance[136].

Withdrawal Rates and Proportion of Patients Receiving the Intended Treatment. Such data ensures equivalence between groups does not result from a high withdrawal or treatment transfer rate in the less responsive group. The data may aid economic analysis even if the arms do not prove equivalent; if a significant number of patients in the combination arm reached pre-defined response criteria, it would suggest cheaper therapy could be used in some cases without detriment.

4.4. Health Economic Assessments.

A comprehensive economic evaluation will assess the cost-effectiveness and cost-utility of the treatment strategies. Given concerns over the costs of TNF-inhibitors to the NHS, a primary economic evaluation will be conducted from the perspective of the health service. As impacts of RA are additionally felt on other sectors of the economy, a secondary economic evaluation will be carried out from a societal perspective to include costs associated with other formal care agencies, lost productivity and social security benefits. The economic evaluation will be integrated into the effectiveness evaluation, with the same criteria adopted for trial eligibility, randomisation and intervention modes. Data on use of resources and other economic impacts

will be collected using a suitably adapted version of the Client Service Receipt Inventory (CSRI), an instrument used successfully in numerous economic evaluations[137], including two studies of arthritis. It will cover socio-demographics, the use of secondary and community-based health and social care services, medications, time off work and receipt of social security benefits (due to all causes because of the complexity of distinguishing comorbidity-related effects).

The CSRI will be administered as a self-complete questionnaire when subjects attend study assessments; there will be an opportunity for staff to check the questionnaire has been completed appropriately and for subjects to ask questions if they do not understand any aspect of it. Resource use directly related to the study treatments (ie dose, frequency and duration of medications and any associated monitoring) will be recorded separately and prospectively by the clinical/research teams to ensure accuracy of this core component of costs. Unit costs will be attached to each resource using the best available estimates of long-run marginal opportunity cost, which will include capital and overhead elements. National unit costs will be used where possible to facilitate generalisability of results, with new local estimations calculated if necessary. Individual-level costs will be summed to estimate total costs from each analysis perspective. Costs will be reported as mean values per treatment group (with variance).

4.5. Definition of the End of the Trial

This will be when the last patient has completed their final assessment.

5 Selection and Withdrawal of Patients

5.1. Inclusion Criteria

a. Males and Females aged over 18 years
b. Established RA by the criteria of the American College of Rheumatology
c. Meet NICE criteria for being prescribed TNF inhibitors
    - Disease Activity Score (DAS) over 5.1 confirmed on at least two occasions 1 month apart
    - Failed trials of two disease modifying anti-rheumatic drugs (DMARDs), including Methotrexate (unless contra-indicated). A trial of a DMARD is defined as being normally of 6 months, with 2 months at a standard dose, unless significant toxicity has limited the dose or duration of treatment
    - No contra-indications to TNF inhibitors (including possibility of pregnancy).

5.2. Exclusion Criteria

a. Unable or unwilling to give informed consent
b. Failure of, or contra-indications to, all proposed DMARD combinations (including possibility of pregnancy)
c. Serious inter-current illness
d. Patients on high dose steroids (in excess of 10mg prednisolone or equivalent per day at trial entry)
e. Current steroid therapy or previous therapy within the last month (oral therapy at a dose in excess of 10mg prednisolone or equivalent per day and/or intra-muscular steroid injections)

5.3. Recruitment Methodologies and Randomisation.

Patients will be recruited from rheumatology clinics in England and Wales, divided into 3 sectors: London/South (responsibility of D Scott and G Kingsley), the Midlands (responsibility of A Hassell) and the North (responsibility of D Walker). We estimate 40 centres will participate and each will enter 5 cases.

Identifying Eligible Patients:

Eligible patients will be identified by rheumatologists and clinic nurses at participating centres. Rheumatologists will approach eligible patients and outline the trial to the patient. If the patient is interested in participating, the patient will be given a patient information sheet to read. The

patient will then be contacted by telephone at least 24 hours after receiving the patient information sheet to see if they are interested in participating in the trial. If they are, a screening visit will be arranged. If a patient does not wish to participate they will be reassured that they routine care will not be affected and a routine appointment will be made.

The Screening Visit & Randomisation:
If the patient is happy to participate in the trial, informed consent will be obtained at the start of the screening visit.

As part of screening, and in line with NICE guidance, the following checks will be made to ensure that patients eligible to receive TNF inhibitors on the grounds of failing at least two DMARDs have no contra-indications to TNF inhibitors:

- Ensure they have failed adequate treatment with two DMARDs and have a DAS-28 greater than 5.1.
- Negative screen for tuberculosis including chest x-ray (and other local measures like Mantoux testing where applicable)
- Repeat DAS-28 to ensure it remains greater than 5.1, four weeks after initial DAS assessment.

The screening assessment pages will be completed anonymously using the Electronic Data Capture (EDC) system, using only the patient's initials and date of birth as identifiers. Once complete and if the patient is eligible, the EDC system will automatically assign consecutive patient numbers to patients in chronological order when they passed the screening assessment. Randomisation numbers will be formed of 4 numbers and prefixed by the region identifier i.e. 1 for London and the South, 2 for the Midlands and 3 for the North. Staff at individual centres and the trial co-ordinator will be unaware of the allocation sequence. The allocation sequence for randomisation will be generated by the EDC system and randomisation will be stratified by region.

Once a randomisation number has been allocated the EDC system will automatically inform the Researcher and the trial co-ordinator by email. The trial co-ordinator will inform Pharmacy at site of the randomisation.

The patient can then be informed that they have been recruited to the trial and the baseline assessment arranged.

As part of screening, we will collect data on:
- patients who are potentially eligible to receive TNF inhibitors
- reasons patients choose not to enter the RCT (insufficient disease activity, non-consent and other reason).
- numbers of patients randomised

Baseline Assessment:
Delays between screening and baseline are to be expected due to the pragmatic nature of the trial and local practices relating to the supply and delivery of TNF inhibitors. Patients may require additional treatment between the screening and baseline assessments i.e. IM steroid injection. The following rule should be applied:
- Patient given appropriate dose of IM steroid
- Baseline assessment delayed for 1 month after date of injection

Eligibility based on a DAS-28 score of greater than 5.1 at screening will not be required to be maintained at the baseline assessment as this is not a requirement for receiving TNF inhibitors in routine practice.

5.4. Withdrawal

As with all clinical trials patients will be free to withdraw at any time. If patients do wish to withdraw they will be invited to remain under observation so that changes in their disease can be assessed; it will be made clear to them that this is entirely at their own discretion.

This is a pragmatic trial following complex national treatment protocols and specific protocols for the treatment involved and it is highly likely that many patients' treatment will be changed according to these protocols, as outlined below.

6 Treatments Involved

6.1.Trial Drugs

There will be two treatment algorithms, (a) for TNF inhibitors and (b) for combination DMARDS. Treatments will be individualised and will depend on patients' responses. Appendix I shows examples for patients with good and poor responses.

TNF inhibitors: All 3 licensed agents - adalimumab, etanercept, and infliximab - will be allowed at standard doses (British National Formulary). The choice of TNF inhibitor will reflect patient's preferences and local circumstances. Methotrexate will also be given to maximise efficacy and (in the case of infliximab) reduce anti-chimeric antibodies. Any patient intolerant to methotrexate may take another DMARD. DAS scores at 3 and 6 months will define responses to therapy.

Patients will have their TNF inhibitor stopped and will be potentially withdrawn from the treatment arm for three reasons:

- *Lack of effect* - as defined by NICE criteria ie change in DAS <1.2 at 6 months
- *Adverse event*- which in the opinion of the supervising specialist necessitates treatment withdrawal
- *Patient initiated*- patients may stop therapy for any reason should they wish (reasons to be specified if patient willing)

Patients in whom one TNF inhibitor is stopped will be able to start another; this option, though controversial, represents current UK practice. Patients who fail two TNF inhibitors for whatever reason will not be able to start a third agent and will require alternative treatment; usually this will be combination DMARDs.

The principles of the treatment algorithm will comprise the following:

- Start TNF inhibitor of choice on the basis of local circumstances and patients preferences
- Assess at 6 months: no change if good response (≥1.2 fall in DAS); change to second TNF inhibitor if <1.2 fall in DAS
- Change in treatment after 6 months will be at the rheumatologist's discretion but would normally be after two consecutive DAS scores > 5.1. Options would be change to second TNF inhibitor or if two TNF inhibitors already given change to DMARD combination or other therapy.

Combination DMARDs: DMARDs from the following list will be used: methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, ciclosporin, azathioprine, penicillamine and gold injections (sodium aurothiomalate) in combinations with proven efficacy over DMARD monotherapy in RCTs. For example:

- Triple therapy with methotrexate (methotrexate-sulfasalazine-hydroxychloroquine)

- Other methotrexate combinations (methotrexate-ciclosporin, methotrexate-leflunomide and methotrexate-gold)
- One sulfasalazine combination (sulfasalazine-leflunomide)

The DMARD combination chosen on trial entry must differ to combinations used prior to trial entry.

Additional monthly steroids (IM depomedrone (120mg stat) or equivalent) will also be used if needed up to a maximum of 6 in the 1 year trial period.

DMARD combinations may be stopped and patients withdrawn from treatment for 3 reasons: adverse events and patient initiated withdrawals (which are identical to those reasons for stopping a TNF inhibitor), and also for lack of effect (change in DAS <1.2) which is similar to that with a TNF inhibitor and will be implemented at 6 months (see below).

The principles of the treatment algorithm will comprise the following:
- Initially: (a) maximise initial DMARD/optimise administration (e.g. parenteral methotrexate); (b) start second/third DMARD; (c) give IM steroid (if appropriate)
- Second step: maximise dose of second/third DMARD
- Third step; change combination (can be repeated if needed)
- Additional option: continue IM steroid injections monthly short-term if RA remains active (maximum of 6 in 1 year trial period)
- Assess monthly and change treatment if change in DAS <1.2 or DAS >3.2
- At 6 months start a TNF inhibitor if change in DAS <1.2
- After 6 months patients may be switched to TNF inhibitor therapy at the rheumatologist's discretion but would normally be after two consecutive DAS scores > 5.1.

The target doses of different DMARDs to be used in combinations will be as follows:
- Methotrexate: 25mg weekly – preferably parenteral though could be oral (achieved by 5mg increments)
- Sulfasalazine: 3gm daily (starting at 500mg daily and increasing by 500mg increments)
- Hydroxychloroquine: 400mg daily (starting at 200mg and increasing as one increment)
- Ciclosporin: 3.5mg/kg (starting at 2mg/kg and increasing incrementally depending on creatinine levels)
- Leflunomide: 20mg/day (staring at 10mg/day and not increasing if used in combination with methotrexate)
- Azathioprine: 100 mg daily (starting at 50 mg and increasing as one increment)
- Penicillamine: 375 mg daily (starting at 125 mg and increasing by 125 mg increments)
- Gold: 20mg/month (starting with test dose, then 50mg/week for 20 weeks, then 50mg/month)
- IM steroid can be given at an appropriate dose for 3 months; further courses may be given if the RA is still active.

Dose adjustments to all drugs will depend on both disease activity and evidence of adverse events. Decisions about changes in treatment will be made by the supervising rheumatologist, but all changes will be reviewed by the chief investigator (D Scott) or local co-applicants (G Kingsley and E Choy) to ensure the algorithm is followed. Should supervising rheumatologists diverge from the algorithm, in particular by giving insufficient therapy in patients with active disease without major adverse effects, the principal investigator will review the decisions with the individual supervising rheumatologist.

The summary of product characteristics for all medications listed above are included in Appendix 1.

6.2 Concomitant Therapy

Non-opiate analgesics and non-steroidal anti-inflammatory drugs will be used as needed at standard doses. Patients taking methotrexate will have folic acid (5mg/wk) to limit adverse events. Patients taking steroids will have bone protection (e.g. alendronate and calcium/vitamin D). Other drugs (e.g. anti-hypertensives) will be used as needed. Patients taking oral prednisolone up to 10mg at entry will stay on treatment. Intra-articular steroids will be used as required and the site and dose of these injections will be recorded. Injected joints will be treated as 'swollen' and 'tender' in DAS28 joint counts for 6 weeks after the injection.

6.3 Interruption of Trial Medication

A temporary interruption in trial medication of up to 8 weeks (consecutive) will be permitted if an adverse event or other unforeseen circumstance, deemed by the Principal Investigator to require stoppage of trial medication, has occurred. This will include:

- stoppage of all trial medication or
- treatment with DMARD monotherapy only or
- treatment with a TNF inhibitor with no accompanying DMARD.

7 Assessment Of Efficacy

7.1. Outcomes

Primary Outcome: change in HAQ scores at 12 months

Secondary Outcomes (collected at 6 and 12 months):

a. Changes in SF-36 and EQ5D
b. The number of patients developing new erosions and changes in the Larsen score
c. Changes in DAS-28, including patients showing good responses (change in DAS ≥1.2) or entering remission (DAS≤2.6)
d. SF-36-based QALYs and EQ5D-based QALYs
e. Client Service Receipt Inventory (for costs)
f. Adverse events and withdrawals (inefficacy, adverse events or other reasons).
g. HAQ score at 6 months

7.2. Timing of Clinical Outcomes

Patients will be screened and then assessed at baseline with outcomes assessed 6 and 12 months. Patients will be assessed irrespective of what treatments they are taking.

7.3. Measurement Of Cost-Effectiveness And Cost-Utility

The cost-effectiveness analysis will combine total average costs (from each perspective) with the primary outcome measure (HAQ) in the form of ICERs to represent additional cost per point improvement on the HAQ. Similarly, the cost-utility analysis will combine costs with utility-weighted quality of life outcomes to explore the additional costs per additional quality-adjusted life-year (QALY) (again from each perspective). Health states will be measured at each assessment point using the SF-36. Utility weights associated with these states will be calculated (via the SF-6D) using an algorithm based on preference weights estimated in a UK population sample[138]. Health state descriptions will also be collected using the EQ5D. Utility weights from another UK general population survey[139] will be attached to these.

This will allow the comparison of utility estimates obtained from the two measures. Sensitivity analyses will be employed to explore the consequences for the results of any key assumptions that need to be made in conduct of the economic evaluation (e.g. concerning unit costs). Uncertainty around the cost-effectiveness and cost-utility of the two treatment strategies will also be explored using cost-effectiveness acceptability curves (CEACs) based on the net benefit approach[140]. These will indicate to the decision-maker what is the likelihood of each treatment

strategy being cost-effective relative to the other given different (implicit monetary) values placed on incremental improvements in the HAQ and QALYs.

8 Assessment Of Safety

8.1. Safety Monitoring

This will follow national guidelines[135] with monthly blood counts and liver function tests plus renal function (creatinine), urinalysis and blood pressure recording for some DMARDs. Patients will be screened for tuberculosis. Patients will be carefully monitored to ensure there is no evidence of infections, in line with current routine practice; no special specific monitoring for infections will be employed.

8.2. Pharmacovigilance

The sponsor (KCL) has delegated responsibility for pharmacovigilance to the Chief Investigator. Any adverse event considered as 'Serious' will be reported within 24 hours of knowledge to the Chief Investigator. It will be assessed for 'Causality' in relationship to trial medication and 'Expectedness' by both the Principal and Chief Investigators. Serious adverse events (SAEs) and serious adverse reactions (SARs) will be reported following the requirements of ENTR/CT 3. Detailed guidance on the collection, verification and presentation of adverse reaction reports arising from clinical trials on medicinal products for human use Revision 2, 2005.

For the purpose of this trial those events or reactions listed in the Summary of Product Characteristic for Methotrexate, other DMARDs and TNF-inhibitors in the most current version of the British National Formulary will not be considered as unexpected.

9 Statistics

9.1. Proposed Sample Size

Our proposed trial seeks to show equivalence between treatment strategies; in this setting the calculation of sample size is more complex than in conventional trials intended to show one treatment is superior. One specific issue is that high cost treatments like TNF inhibitors can only be justified if they show substantial benefits over conventional inexpensive treatments. Key issues in this respect are the extent to which a difference in HAQ (the primary outcome) between groups is clinically relevant, the degree of certainty in avoiding a Type II error, and the degree of conservatism in the statistical approach taken. The final sample size calculation has taken into account these various considerations.

This study is designed to address the following hypothesis: treating active RA patients who have failed to respond to two DMARDs with intensive conventional treatment using combination DMARDs and steroids gives equivalent results to treatment with TNF-inhibitors. The sample size calculation has been based on changes in HAQ scores in:

a. the ATTRACT trial[38] (infliximab in RA) in which the mean HAQ score at baseline was 1.7, reduced after treatment by 25%; the SD of the change in HAQ was 0.4;
b. the CARDERA (Combination Anti-Rheumatic Drugs in Early Rheumatoid Arthritis) trial, an MRC funded UK trial of 464 patients led by the applicants (presented at the Association of Physicians in April 2006) in which the mean HAQ score at baseline was 1.6, reduced after treatment by 31%; the SD of the change in HAQ was 0.6.

We have taken the average SD for changes in HAQ scores in these two trials, estimated at 0.5.

The minimally clinically important change in HAQ in RA is considered to be 0.22. The trial will therefore be designed under the assumption that DMARD and TNF treatments produce

equivalent reductions in HAQ and that a difference of less than 0.22 will be regarded as equivalence.

Formally, the trial will be designed to test the null hypothesis of a difference greater than 0.22. With a (one sided) testing level of 5%, a sample size of 176 is required to achieve 90% power. To allow for a dropout of 5-7%, we will recruit 190 patients.

9.2. Main Analysis

The primary outcome for the trial, the 12 month change in HAQ score, will be examined through a general linear model regression analysis stratified by region and sex. A confidence interval will be derived for the difference in HAQ reduction between the two treatment arms. If a difference of more than 0.22 is excluded from the interval then the treatments will be regarded as equivalent. Additional analyses will extend the regression analyses to include other explanatory variables, including baseline HAQ score. Other outcomes will be examined through comparable regression methods with the choice of model from the class of generalized linear models being determined by the nature of the outcome variable. The study data will be analysed on both a per protocol and intention to treat basis. Sensitivity to missing data will be examined by comparing analyses based on observed data, last observation carried forward and linear increment analysis.

9.3. Economic Analyses

These will be conducted on an intention-to-treat basis. As cost data are expected to be non-normally distributed, non-parametric bootstrap methods will be used to obtain 95% confidence intervals around mean cost differences between the treatment arms and for the net benefit analyses for the estimation of cost-effectiveness acceptability curves. Comparisons of mean costs, net benefits (and outcomes for the calculation of incremental cost-effectiveness ratios, ICERs, and net benefits) will be adjusted for baseline costs/outcomes to provide more relevant treatment-effect estimates[141].

10 Source Data And Documents

10.1. CRFs

Where information is collected directly from the participant, the CRF will be considered the source data document. When trial data is taken from information in original documents, the source data will be verified according to procedures set out in Section 11 to ensure that trial data is agreement with the original document. Comprehensive training will be given to individuals completing trial documents.

10.2. Retention of Trial Documentation

All documents will be retained as strictly confidential at the Investigator's site for at least 15 years after completion/discontinuation of the trial. Trial data will be stored in a lockable, fireproof container. Computers and databases will be password protected. Access will be granted for trial related monitoring by the sponsor and for auditing and regulatory inspection purposes.

11 Quality Control and Quality Assurance

11.1. Complying with 'The Medicines for Human Use (Clinical Trials) regulations 2004'

Kings College Rheumatology Department and collaborating units are experienced in clinical trials. Departmental standard operating procedures are based on recent guidance from the NHS Research Ethics Committee and encompass the requirements of ICH Good Clinical Practice guidelines, the European Clinical Trials Directives 2001/20/EC, the GCP Directive 2005/28/EC and UK Medicines for Human Use (Clinical Trials) Regulation 2004.

Research staff will attend an induction program that includes Good Clinical Practice training, protocol familiarisation, an introduction to the departmental Standard Operating Procedures for trials and any other training necessary to ensure that the trial is compliant with the applicable governance and regulations. Regular internal monitoring will be undertaken to ensure standards are met.

The Trial Management team will ensure good record keeping and accurate data capture by organising frequent monitoring of sites to source data verify data according to guidelines set out in the Department of Academic Rheumatology's Standard Operating Procedure for Monitoring of Clinical Trial Data. The level of monitoring will be agreed between the Chief Investigator and Trial Steering Committee based on the trials risk assessment prior to recruitment commencing.

12 Ethical Issues and Risk Assessment

12.1 Risks and Anticipated Benefits for Trial Participants and Society

Equipoise: equipoise, or the uncertainty principle[142], is a key requirement for RCTs in which the best treatment must be unknown[143] so participants do not suffer harm by assignment to one arm[144]. Alternative ethical approaches to RCTs[142] have not gained universal acceptance[145,146] and strategies like equipoise-stratified randomisation are not widely used[147].

Equipoise in individual patients reflects not only the scientific probabilities of particular outcomes (known to trial clinicians) but also the value individuals place on particular outcomes or risks (known only to individual patients). The solution to varying individual patient equipoise is open genuine consultation with each about the choices using clear written information; similar approaches can be used with referring clinicians. It is difficult to ascertain the level of equipoise across the patient community due to the wide variability of patients' perspectives[148] on side effects and varying views on the severity and ultimate of RA[149].

Community equipoise is essential for an RCT to be ethical. We consider there is sufficient equipoise among rheumatologists on when to use TNF inhibitors to justify our proposed RCT. Rheumatologists vary markedly in prescribing these agents only partly for financial reasons. Discussion with consultant rheumatologists suggests that TNF inhibitors are felt to be highly effective but there is debate on which patients should receive them (in terms of severity and stage of disease), on their long-term risks and benefits and on their advantages over maximal existing therapy[119]. There is also uncertainty, especially among public health clinicians, about their cost effectiveness.

Current Access to TNF Inhibitors: marked variability was shown in a recent survey (Apr-Jun 2006) by the Arthritis and Musculoskeletal Alliance (ARMA), a charitable umbrella organisation representing patient and professional views in rheumatology. 81 of 106 (76%) rheumatology units participated[150]. 20% reported they could not prescribe TNF inhibitors to all RA patients meeting NICE criteria and had 10-126 patients waiting. 15% had caps on the number of patients they could give TNF inhibitors. Some units could only treat small numbers (around 10) patients while others could treat 500 patients.

Concerns for Patients Entering this Trial: apart from general concerns about randomisation, especially for individuals who do not perceive true equipoise between treatments, there is a specific emotive concern about "entitlement" to anti-TNF agents. Initially many UK patients believed that, compared to the USA and continental Europe, they were deprived of these agents on financial grounds. This was exacerbated by intense pharmaceutical involvement with clinicians and some patient organisations and by media presentation of these agents as "miracle cures". Unlike normal new drugs, there was no counter-information about existing alternatives, like combination DMARDs because these are inexpensive and out of patent. As access to TNF

inhibitors remains variable, patients and clinicians may perceive the proposed trial as an additional means of inhibiting access. However, a strategy is needed as biologics cannot be given “on demand” in our resource-limited health system, due to their long-term costs (reflecting high production costs), the need for indefinite treatment, their uncertain cost-effectiveness, and the many new biologics coming on-stream (e.g. abatacept and rituximab).

Public Issues and Concerns: an acceptable appropriate strategy to rationalise access to TNF inhibitors requires high-quality evidence to inform NICE about their effective use; this was recognised by NIHR Board Members in their response to our outline application. Good information for patients and referring clinicians is needed to explain the importance of the trial in developing a strategy for fair and equitable TNF inhibitor access across the nation to those who will benefit most. A national strategy for using TNF inhibitors should be developed by a wide range of patients, the public and clinicians based on sound clinical evidence. This trial, and the associated consultations, will assist in starting this debate.

The adoption of new agents goes through several phases. Initially they are considered safe and effective. Adverse events are underestimated at this stage, reflecting selective recruitment to clinical trials, careful patient follow up in trials, the expertise of the research clinicians and the small number of patients treated; efficacy is over-estimated for similar reasons. The next phase of drug adoption involves a reaction against the agent precipitated by unexpected side effects and recognising the agent does not fulfil all its initial promise. TNF inhibitors are leaving the initial phase as many patients do not respond, those who do require continuing treatment and large studies have been published describing more accurately rare, serious complications like infection and cancer. They now need to enter the final stage of drug adoption, where their advantages and disadvantages are seen in a balanced light. We believe our trial is therefore timely from the perspective of both patients and recruiting clinicians.

12.2. Informing Potential Participants of Benefits and Risks

Potential participants will be identified by rheumatologists and specialist nurses in routine clinics at participating centres. They will receive a brief summary of relevant information about the trial including key risks and benefits. Those patients who are interested will receive a full Patient Information Sheet explaining in plain English the purpose of the study and the actual and potential risks and benefits of DMARD combination therapy compared to treatment with TNF inhibitors. The Patient Information Sheet will be drawn up by the Investigators and patient representatives based on the analysis of risks and benefits in this application; advice will be sought from the full trial patient representatives group and the Trial Steering Committee before submission to the relevant Research Ethics Committee.

12.3. Obtaining Informed Consent

Written informed consent will be sought in line with guidance from the NHS Research Ethics Committee. Consent will be sought by a trial investigator or appropriately qualified delegated person at an informed consent interview; patients will be encouraged to have a friend or relative present if they wish. All relevant facts will be discussed including any patient concerns. The study will not involve vulnerable groups.

13 Governance, Data Handling And Record Keeping

13.1. Institutional Sponsorship

Kings College London will provide institutional sponsorship for the trial.

13.2. Day to Day Management

The Chief Investigator and Principal Applicants will be responsible for daily management with the Trial Co-ordinator. They will meet weekly during the setting up phase and fortnightly when

data collection is underway and will inform the Trial Management Committee of progress, recruitment, problems and adverse events.

The Trial Co-ordinator will be based in the Department of Academic Rheumatology, King's College London, Denmark Hill with the Principle applicants. He/she will be responsible for the day to day running of the trial and will ensure that necessary regulatory and ethical approvals are obtained and that the trial is run in accordance with the approved protocol. He/She will also be responsible for: monitoring the results of screening assessments, (with the applicants when necessary), and deciding on the suitability of patients to be entered into the trial, monitoring recruitment and withdrawal rates, progress and safety reporting according to the time frames and procedures set out by the Medicine for Human Use Regulations (2004), the distribution and maintenance of trial materials and keeping applicants and committees informed of all necessary aspects of the trial.

With the assistance of the *Data Manager*, the Trial Co-ordinator will also ensure that data is handled and managed efficiently by following Department of Academic Rheumatology's Standard Operating Procedure for Data Management. Two independent members of the trial team will check the data. Discrepancies or omissions will be obtained within time frames set out in the SOP. The Trial Co-ordinator and Data Manager will also ensure that data is treated confidentially and held securely to guarantee compliance with the Data Protection Act.

A *Principle Investigator* will be designated at each participating site. He/she will be responsible for the conduct of the trial at his/her centre and will liase with the Trial Co-ordinator and Chief Investigator to ensure that the trial is run in accordance with the trial protocol.

Trial Management Committee: This will meet every 3 months to review progress and address and deal with any problems. It will inform Data Monitoring and Ethics and Trial Steering Committees of the progress of the trial. Although the centres involved will be able to achieve full recruitment, since this trial is part of the ARC/BSR Trials Initiative, other collaborators will be welcomed and actively encouraged to join the trial.

13.3. Trial Steering Committee

This will meet every 6-12 months during the trial. The independent chair is Professor Peter Maddison (Bangor) an established clinical trial expert in RA. There will also be independent rheumatologists, a patients' advocate, the applicants and collaborators.

13.4. Data Monitoring and Ethics Committee

This will assess trial progress, occurrence of adverse events and all other aspects. It will meet 6 monthly for the duration of the trial. The independent chair is Professor Deborah Symmons,who is Director of the arc Epidemiology Unit and a member of the arc Data Monitoring and Ethics Committee. At least 2 other independent members will be invited to join, including a statistician.

14 Financial And Insurance Matters

The costs of the trial will be covered by Health Technology Assessment (HTA) funding. This trial has been included on the National Institute for Health Research (NIHR) Clinical Research Portfolio and therefore additional funding can be obtained by each site from their local Clinical Research Network.

For performance of the Clinical Study obligations by a NHS Trust the Sponsor shall pay the sums set out in the attached Clinical Study Agreement in accordance with the terms and conditions set out the agreement.

Trial participants and staff working on the trial will be fully insured. Negligence will be covered by the participating NHS Trust's insurance. King's College London indemnity will cover non-negligent harm including that arising from the design of the research.

15 Publication Policy

The Chief Investigator will ensure that on completion of the trial the results are analysed, written up, reported and disseminated. Trial findings will be submitted to a peer-reviewed journal, irrespective of the results of the trial. The trial's ISRCTN number will be quoted on all publications.

16 Supplementary Information

A CONSORT flow chart and a treatment algorithm are attached as appendices.

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18 Appendices

Appendix I: Examples Of Treatment Algorithms In TACIT Trial

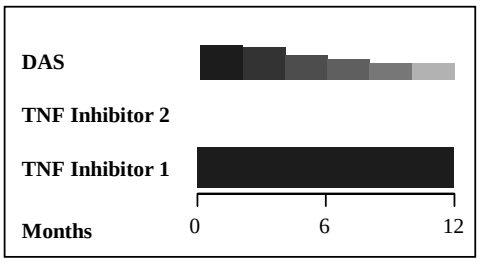
A: Patients Randomised To Receive TNF inhibitors

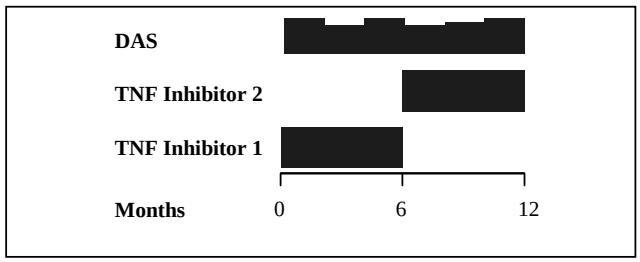
A1: Successful Treatment

- Initially start TNF inhibitor 1
- *DAS* *falls >1.2 by 6 months*
- Thereafter therapy maintained

A2: Unsuccessful Treatment

- Initially start TNF inhibitor 1
- *DAS* *remains high prior to 6 months*
- Month 6 stop TNF inhibitor 1
start TNF inhibitor 2
- *DAS* *remains high prior to 12 months*
- Up to month 12 stop TNF inhibitor 2
- Thereafter DMARD combination or withdraw





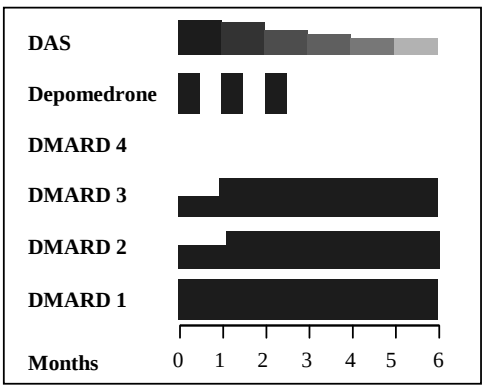
B: Patients Randomised To Receive Combination DMARDs

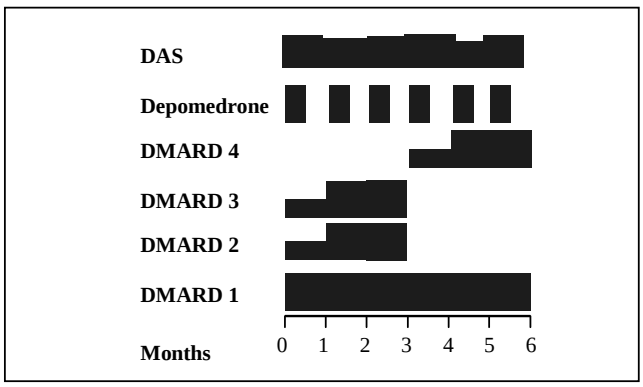
Successful Treatment

- Initially maximise existing DMARD
start 2nd & 3rd DMARDs
IM Depomedrone
- Months 1/2 increase 2nd & 3rd DMARDs
IM Depomedrone
- *DAS* *falls >1.2 by 3 months*
- Thereafter therapy maintained

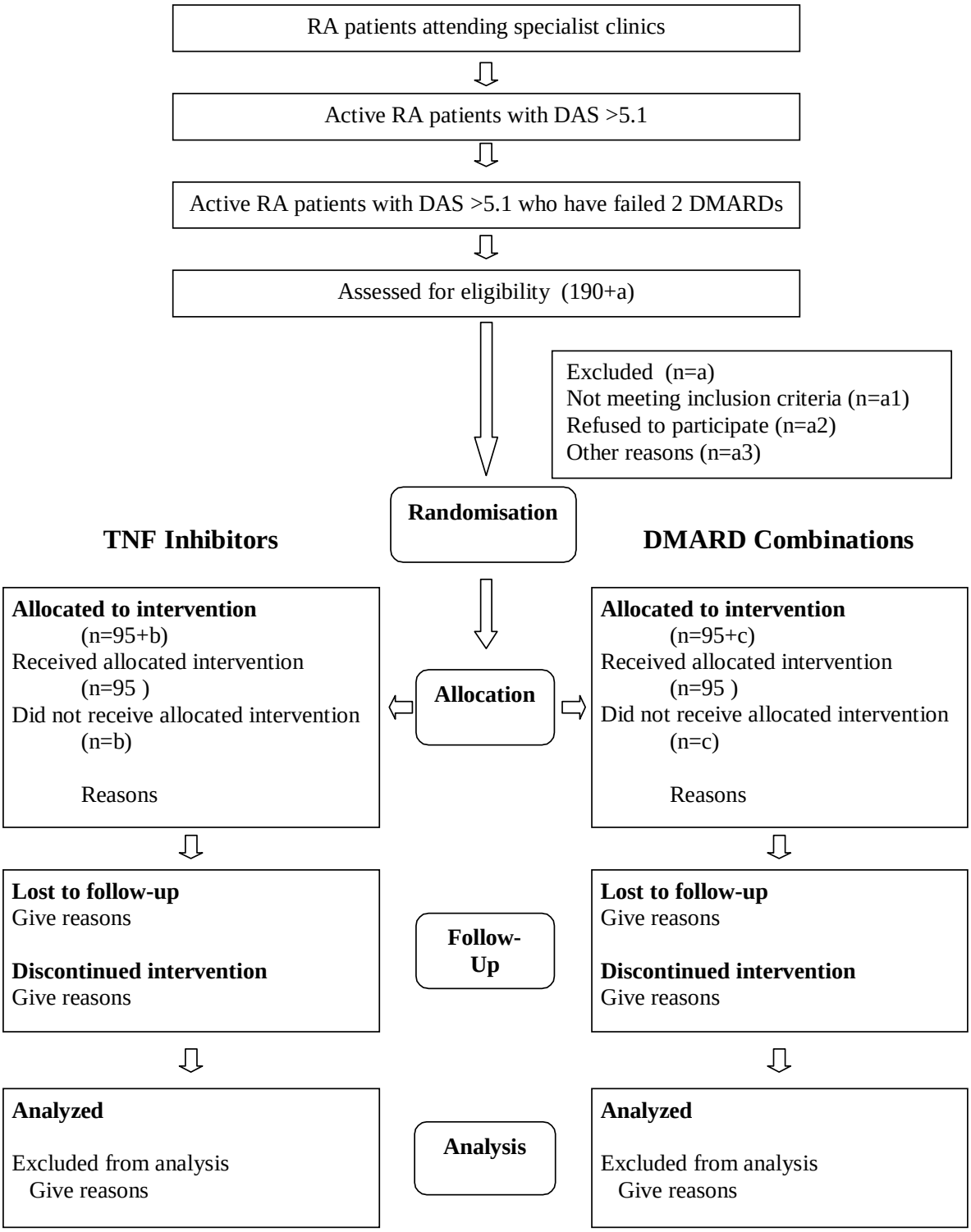
Unsuccessful Treatment

- Initially maximise existing DMARD
start 2nd & 3rd DMARDs
IM Depomedrone
- Month 1/2 increase 2nd & 3rd DMARDs
IM Depomedrone (if appropriate)
- *DAS* *remains high at 3 months*
- Month 3 stop 2nd & 3rd DMARDs, start 4th DMARD
- Month 4 increase 4th DMARD
- *DAS* *remains high at 6 months*
- Month 6 stop DMARD combinations
- Thereafter TNF inhibitor





Appendix II: Preliminary CONSORT flowchart For TACIT Trial



Notes: a = patients excluded (for reason a1-a3)
Patients randomised to receive treatment but who did not receive intervention: b= TNF inhibitors; c= DMARD combinations