1 Randomised controlled trial of tumour-necrosis-factor inhibitors against combination intensive therapy with conventional disease modifying anti-rheumatic drugs in established rheumatoid arthritis: TACIT Trial

Test drug: Tumour necrosis factor inhibitors (TNFis) versus combination disease modifying anti-rheumatic drugs (cDMARDs)

Name of the sponsor:
NIHR-Health Technology Assessment (HTA) Grant Number 06-303-84

Protocol identification: 2007-001190-28

Open-label, pragmatic, randomised, multicentre, two-arm trial

Study initiation: 1st September 2008

Termination date: None

Study completion date: 14 December 2011

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Sponsor details: King's College London, Strand, London, WC2R 2LS.

GCP statement: All staff were suitably trained to perform their roles in the trial. The study was conducted in accordance with Good Clinical Practice and all essential documents will be archived for at least 5 years.

Report date: March 2013

2 SYNOPSIS

Name of Sponsor: NIHR-HTA	Individual Study Table Referring to Part of the Dossier Volume: 1 Page:	*(For National Authority Use only)*
Name of Finished Product: None		
Name of active ingredient: TNF inhibitors and combination DMARDS		
Title of Study: Randomised controlled trial of tumour-necrosis-factor inhibitors against combination intensive therapy with conventional disease modifying anti-rheumatic drugs in established rheumatoid arthritis: TACIT trial		
Investigators: Professor David L Scott, Kings college hospital Dr Gabrielle Kingsley, Lewisham Hospital Dr Khalid Ahmed, Princess Alexandra Hospital Dr Sandra Green, Weston General Hospital Dr Anurag Bharadwaj, Basildon University Hospital Dr Fraser Birrell Wansbeck, General Hospital Professor Kuntal Chakravarty, Queens Hospital, Romford Dr Gerald Coakley, Queen Elizabeth Hospital, Woolwich Professor Andrew Cope, Guy's Hospital Dr Christopher Deighton, Derby City General Hospital Dr Karen Douglas, Russell's Hall Hospital Dr Sarah Medley, Orpington Hospital Dr Tania Gordon, Southend University Hospital Dr Clive Kelly, Queen Elizabeth Hospital Dr Namita Kumar, University Hospital of North Durham Dr Ramasharan Laxminarayan, Queen’s Hospital, Burton Dr Jon Packham, Haywood Hospital		

Dr Ira Pande, Queens Medical Centre Dr Michael Plant, James Cook University Hospital Dr Selwyn Richards, Poole Hospital Dr Euthalia Roussou, King George's Hospital Dr Thomas Sheeran, Cannock Chase Hospital Dr Karen Walker-Bone, Royal Sussex County Hospital Dr Christopher Erdhardt, Orpington Hospital Dr Atheer Al-Ansari, Weston General Hospital	
Publication (reference): TITLE: Randomised controlled trial of tumour-necrosis-factor inhibitors (TNFi's) against combination intensive therapy with conventional disease modifying anti-rheumatic drugs (cDMARDs) in established rheumatoid arthritis (RA): the TACIT trial David L. Scott, Fowzia Ibrahim, Clive Kelly, Fraser Birrell, Kuntal Chakravarty, David Walker, Peter Maddison, and Gabrielle Kingsley: **Abstract accepted as oral presentation at British Rheumatological society conference April 2013**	
Studied period (years): 2008-2011 **(date of first enrolment):** 14 September 2008 **(date of last completed):** 14 December 2011	**Phase of development**: III
Objectives: The overall objective was to assess whether RA patients eligible to receive TNFis achieve similar outcomes with patients treated with cDMARDs.	
Methodology: An open-label, 12-month pragmatic, randomised, multicentre, two-arm trial	
Number of patients (planned and analysed): The number of patients planned was 190 and the number analysed was 205.	

Diagnosis and main criteria for inclusion:

1. Males and Females aged over 18 years
2. Established RA by the 1987 criteria of the American College of Rheumatology [5]
3. Disease duration of at least 12 months
4. Meet NICE criteria for being prescribed TNF inhibitors [81]
   a. Disease Activity Score for 28 joints (DAS28) over 5.1
   b. Failure to respond to two disease modifying anti-rheumatic drugs (DMARDs) including methotrexate
   c. No contra-indications to TNF inhibitors (including possibility of pregnancy).

Test product, dose and mode of administration, batch number:

TNF Inhibitors

The 3 licensed agents available when the trial started- adalimumab, etanercept, and infliximab –were allowed at standard doses (British National Formulary). The choice of TNF inhibitor reflected patient's preferences and local circumstances. Methotrexate was also given to maximise efficacy and (in the case of infliximab) reduce anti-chimeric antibodies. Patients intolerant to methotrexate took another DMARD. DAS28 scores at 3 and 6 months defined responses to therapy.

Patients had their TNFi stopped for one or more of three reasons:

1. Lack of effect as defined by NICE criteria i.e. change in DAS28 <1.2 at 3 or 6 months
2. An adverse event which, in the opinion of the supervising specialist, necessitated treatment withdrawal
3. Patients could stop therapy for any reason should they wish (reasons to be specified if patient willing)

Patients in whom one TNFi was stopped were able to start another. This option represented current UK practice when the trial started. Patients who failed two TNFis for whatever reason were not able to start a third agent and required alternative treatments such as combination DMARDs.

The principles of the treatment algorithm were as follows:

a. Starting a TNF inhibitor of choice on the basis of local circumstances and patients preferences
b. Assessed at 6 months: no change if good response (≥1.2 fall in DAS28); changed to second TNFi if <1.2 fall in DAS28; if two biologics already given and DAS28 change <1.2 TNF inhibitor stopped and patient offered DMARD combination or other therapy.
c. Change in treatment after 6 months at the rheumatologist's discretion but would normally be after two consecutive DAS28 scores > 5.1. Options were change to second TNF inhibitor or if two TNF inhibitors already given change to DMARD combination or other therapy.

Duration of treatment:

Treatment lasted for 12 months

Reference therapy, dose and mode of administration, batch number:

Combination DMARDs

Those with proven efficacy over DMARD monotherapy in randomised controlled trials were used including:

a. Triple therapy with methotrexate (methotrexate-sulfasalazine-hydroxychloroquine)
b. Other methotrexate combinations (methotrexate-ciclosporin, methotrexate-leflunomide and methotrexate-gold)
c. One sulfasalazine combination (sulfasalazine-leflunomide)
d. Additional monthly steroids (IM depomedrone (120mg stat) or equivalent) were used if needed.

DMARD combinations were stopped 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 DAS28 <1.2) which is similar to that with a TNF inhibitor but was only be implemented at 6 months.

The principles of the treatment algorithm comprised the following:

1. Initially: maximising initial DMARD/optimise administration (e.g.

parenteral methotrexate); start second/third DMARD; (c) give IM depomedrone (whenever possible)

2. Second step: maximising dose of second/third DMARD
3. Third step; change combination (repeated if needed)
4. Additional option: continue IM depomedrone monthly short-term if RA remains active
5. Assess monthly and change treatment if change in DAS28 <1.2 or DAS28 >3.2
6. At 6 months start a TNF inhibitor if change in DAS28 <1.2
7. After 6 months patients could be switched to TNF inhibitor therapy at the rheumatologist's discretion but would normally be after two consecutive DAS28 scores > 5.1.

The target doses of different DMARDs used in combinations was as follows:

1. Methotrexate: 25mg weekly – preferably by IM injections though could be oral (achieved by 5mg increments)
2. Sulfasalazine: 3gm daily (starting at 500mg daily and increasing by 500mg increments)
3. Hydroxychloroquine: 400mg (starting at 200mg and increasing as one increment)
4. Ciclosporin: 3.5mg/kg (starting at 2mg/kg and increasing incrementally depending on creatinine levels)
5. Leflunomide: 20mg/day (staring at 10mg/day and not increasing if used in combination with methotrexate)
6. Gold: 20mg/month (starting with test dose, then 50mg/week for 20 weeks, then 50mg/month)

IM depomedrone given as 120mg/month for 3 months; further courses were given if the RA was still active.

Criteria for evaluation:

Efficacy: Treating active RA patients who have failed to respond to two DMARDs with cDMARDs and steroids gives equivalent results to treating with TNFis.

Safety: During the study period patients were monitored for any adverse

events

Statistical methods:

Analyses used Stata (version 12.0, StataCorp) and the R statistical package (R Development Core Team). Statistical significance was determined at the 5%-level using 2-sided tests.

Baseline characteristics were summarised by randomised group as mean and standard deviation (continuous normally distributed variables), medians and interquartile ranges (non-normally distributed variables), and frequencies and percentages (categorical variables).

Randomised patients who received treatment were assessed on an intention-to-treat (ITT) basis. All missing data was imputed using baseline outcomes and explanatory covariates (treatment group, sex, age, ethnicity, regions and disease duration), assuming measurements were missing at random. 6-monthly outcomes were imputed using the monotone assumption. Monthly outcomes were imputed using multivariate sequential imputation with chained equations. 20 datasets generated by multiple imputations were combined using Rubin's rules [15,16]. Linear increments methods gave similar findings, showing our assumptions were robust [17].

Linear regression evaluated 6-monthly outcomes. Univariate analyses were adjusted for region (design effect) and multivariable analyses were adjusted for gender, ethnicity, age, region, and disease duration and baseline covariates. Generalised estimating equations (GEE) evaluated monthly outcomes; they included baseline values as a covariate with sub-analyses assessing months 1-6 and 7-12. Estimates were presented as mean treatment effects (beta coefficients) with 95% confidence intervals (CI). Serious adverse events were compared using Fisher's exact test.

Summary - Conclusions:

Efficacy Results: 432 patients were screened, 214 randomised and 205 treated (104 cDMARDs, 101 TNFis. 62 (46 cDMARDs, 16 TNFis) patients started/switched TNFi after 6 months. 12-month intention-to-treat analysis

showed statistically greater but clinically equivalent improvement in HAQ (difference on adjusted linear regression 0.15; 95% CI 0.003, 0.31; p=0.047) and EuroQol (p=0.009) and statistically and clinically equivalent changes in SF-36 sub-scores and joint damage. DAS28 fell more rapidly with TNFis but 12-month DAS28 scores were similar. Only 80 patients (cDMARDs 36, TNFis 44) ever achieved DAS28 remissions with 30 (cDMARDs 11, TNFis 19) having sustained remissions (3 consecutive months). cDMARDs cost less (£5,552/patient) and gave equivalent outcomes. Completer analysis confirmed these findings. cDMARD patients remaining on DMARDs or switching to TNFis had similar outcomes. 28 patients (10 cDMARDs, 18 TNFis) had serious adverse events

Safety Results: There were no unexpected adverse reactions

Conclusions: cDMARD algorithm gave equivalent improvements in disability and quality of life to starting TNFis in methotrexate-resistant RA and cost substantially less. Only a minority of patients achieved sustained remission with either treatment. New management strategies are required to improve the effective and cost-effective use of TNFis in RA.

Date of the report: March 2013

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4 LIST OF ABBREVIATIONS AND DEFINITION OF TERMS

ACR	American College of Rheumatology
Adalim	Adalimumab
anti-CCP	Anti-Cyclic Citrullinated Peptide
BMI	Body Mass Index
BSR	British Society For Rheumatology
CCP	Cyclic Citrullinated Peptide
cDMARD	Combination Disease Modifying Anti-Rheumatic Drugs
CEAC	Cost-Effectiveness Acceptability Curve
Certoliz	Certolizumab
CI	Confidence Interval
CRP	C-Reactive Protein
Csa	Ciclosporin
CSRI	Client Service Receipt Inventory
DAS	Disease Activity Score
DAS28	Disease Activity Score for 28 Joints
DMARD	Disease Modifying Anti-Rheumatic Drug
DMEC	Data Monitoring And Ethics Committee
EDC	Electronic Data Capture
EQ5D	EuroQol 5 Dimension
ESR	Erythrocyte Sedimentation Rate
Etan	Etanercept
GEE	Generalised Estimating Equations
Golim	Golimumab
HAQ	Health Assessment Questionnaire
HLA	Human leukocyte antigen
ICERs	Incremental Cost-Effectiveness Ratios
IL1	Interleukin 1
IM	Intra-Muscular
Inflixm	Infliximab
IQR	Inter-Quartile Range
Kg	Kilogram

MCS	Mental Component Score
Mg	Milligram
MRI	Magnetic Resonance Imaging
MTX	Methotrexate
NHS	National Health Service
NICE	National Institute For Health And Clinical Excellence
PCS	Physical Component Score
PGT	Gold Aurothiomalate
QALY	Quality-Adjusted Life Years
RA	Rheumatoid Arthritis
RCT	Randomised Controlled Trial
SD	Standard Deviation
SF-36	Medical Outcomes Study Short Form 36
SPSS	Statistical Product And Service Solutions
SSZ	Sulfasalazine
TNFi	Tumour Necrosis Factor Inhibitor
VAS	Visual Analogue Scale
Wk	Week
WMD	Weighted Mean Differences

5 ETHICS

5.1 Independent Ethics Committee (IEC) or Institutional Review Board (IRB)

NRES Committee London - Bentham (formerly The Joint UCL/UCLH Committees on the Ethics of Human Research Committee A), approval by Local Research Ethics committees and R&D departments at each centre.

5.2 Ethical Conduct of the Study

The study was conducted in an ethical manner in accordance with 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.

5.3 Patient Information and Consent

All enrolled patients gave written informed consent.

6 INVESTIGATORS AND STUDY ADMINISTRATIVE STRUCTURE

6.1 Investigators

Professor David Scott

6.2 Other administrative staff

Dr Anna Kowalczyk, Dr Kim Mahood , Rebecca Brendell , Dr Kelly Gormley, Mrs Beverley White-Alao and Mr Dominic Stringer

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7 INTRODUCTION

7.1 Rheumatoid Arthritis

7.1.1 Key Impacts

Rheumatoid arthritis (RA), one of the commonest disabling diseases in the UK, remains a major healthcare problem [1-3]. It affects almost 1% of UK adults and is more common in women. There are two peak ages of onset, early adulthood (mainly women) and later life (equal sex distribution). There are internationally accepted classification criteria for RA which, from time to time, have been revised and modernised [3-6].

Its main impacts are increasing disability and reduced quality of life [7]. Both are substantial and persistent. They reflect the combined effects of persisting joint inflammation, progressive joint damage and extra-articular features of RA [8]. Another significant impact of RA is reduced life expectancy which is mainly due to associated co-morbidities like coronary artery disease [9]. The final major impact of RA is the substantial costs from medical and social care and from lost employment [10].

7.1.2 Disease Course And Outcomes

The primary clinical feature of RA is chronic, usually persistent, inflammatory synovitis initially mainly affecting the small joints of the hands and feet but subsequently spreading to involve multiple other joints [7]. Without adequate treatment, many patients will develop joint damage, classically erosions, but also joint space loss and secondary osteoarthritis [11]. In addition, RA may be associated with extra-articular features, such as nodules and interstitial lung disease [8], and with co-morbidities, such as the increased risk of cardiovascular disease and infection [12].

Diagnosis combines clinical features with laboratory tests like acute phase markers (ESR and CRP) [13], rheumatoid factor, anti-cyclic citrullinated peptide (CCP) antibodies [14-16] and imaging (ultrasound, MRI and/or X-ray) [17-19]. Definitive differentiation from other forms of inflammatory arthritis is difficult in early arthritis but usually uncontroversial in established disease.

The outcome of RA is highly variable ranging from mild disease with limited impact on a patient's life to severe unremitting disease unresponsive to treatment. Some features are known genetically and epidemiologically to be associated with a poorer outcome including specific HLA genotypes, smoking and the presence of anti-CCP antibodies [20-22]. However, it has proved difficult to develop an outcome predictor at the level of the individual patient which would be required to develop tailor-made individual treatment regimes.

7.1.3 Disease Costs

RA results in high medical and social costs [23]. Drug costs are a significant part of the economic cost. Conventional drugs are relative inexpensive. Newer biological agents are very expensive and over time drug costs have risen substantially. A second cost component is other medical care. These costs are modest in the short-term but rise substantially when surgical treatment or supportive long-term medical treatment is needed for disabling severe RA or for comorbid disease. The final area is social costs. These include loss of work, support from family and carers and costs of care within the community. These social costs usually exceed medical expenses and rise with disease duration and severity.

Historically, in the period before biologic treatments were available, the direct and indirect costs were estimated to be in the region of £55-£70M per million of the population [24]; the disease cost a total of £4 billion for the UK as a whole [25]. Since the introduction of biological treatments drug costs have increased substantially. A report by the National Audit Office in 2008 estimated that RA costs the NHS around £560 million a year in healthcare costs, with the majority of this in the acute sector [26]. This report estimated that the costs to the NHS of biologics for treating RA were around £160 million annually. As biologics prescribing for RA has continued to increase the current costs are likely to be substantially higher but may be balanced by reductions in other medical costs, such as orthopaedic interventions for RA, if high cost drug treatments improve medical outcomes. The National Audit Office Report also estimated that the additional cost to the UK economy of sick leave and work-related disability for RA is £1.8 billion a year.

7.1.4 Assessments

Assessments in rheumatoid arthritis mainly look at joint inflammation. Clinical-based assessments include swollen and tender joint counts and global assessment – which estimates

overall disease activity and health status. Standard joint counts focus on 28 joints in the hands, upper limbs, and knees. Some experts prefer extended 66 and 68 joint counts; these include the feet. Laboratory measures include the erythrocyte sedimentation rate, C-reactive protein, or both. Patient-based measures span pain, global assessment, and disability [27-29]. The health assessment questionnaire (HAQ) measures disability [30]. Other areas, such as fatigue and depression [31, 32], are very relevant to patients but are not always formally assessed. Patient-based measures are especially important because they measure the individual's perspective of the burden of their rheumatoid arthritis.

A number of combined indices amalgamate individual assessments. A widely used combined index in the disease activity score 28 (DAS28), which combines 28 swollen and 28 tender joints (hands, arms, and knees), patient's global assessment, and erythrocyte sedimentation rate to indicate the patient's current status [33]. As calculating DAS28 involves a complex mathematical formula, simplified variants have been devised [34]. The simplified disease activity index uses 28 tender and swollen joint counts, doctors' and patients' global assessments, and C-reactive protein. The clinical disease activity index is similar but omits C-reactive protein. American College of Rheumatology (ACR) improvement criteria, which gauge change in status in clinical trials, include falls in joint counts and several other measures (patient's and doctor's global assessments, erythrocyte sedimentation rate, pain and HAQ. They record 20% (ACR20), 50% (ACR50), and 70% (ACR70) improvements in five of the seven measures [35].

Juxta-articular erosions characterise progressive established RA and are usually irreversible. They can be readily identified on x-rays of the hands and feet. Two typical erosions are sufficient for diagnosis [36]. Extensive damage seen on radiographs suggests RA is inadequately controlled. Rapid progression of joint damage needs intensive treatment [37]. There are several scoring systems to quantify damage on radiographs in research studies. Although new imaging modalities like ultrasound and magnetic resonance imaging can assess structural changes, they are not yet widely used except in research [38].

7.1.5 Treatment Goals

The overall goal is making patients feel better and minimising the impact of RA on their lives [39]. The main immediate treatment goal over the last two decades has been to reduce disease

activity. Reducing joint and systemic inflammation is beneficial in itself. Crucially, it is also associated with other benefits including decreased disability, improved quality of life and reduced progression of joint damage. A dominant theme has been to treat patients with active RA; in the main, current treatments mean that few patients now have persisting active disease.

More recently there has been a shift towards making remission the main goal. An ideal treatment would result in the majority of patients achieving remissions with no active joint inflammation and no functional deterioration or erosive progression [40]. Although 10–50% of patients with early RA can achieve remission [41], only a small minority of established RA patients achieve sustained remissions. An associated difficulty in determining the frequency of remission depends on how it is defined, and the intensity of treatment [42]. At present remission remains a treatment aspiration rather than a clear goal.

Relatively cheap, readily available disease modifying anti-rheumatic drugs (DMARDs) like methotrexate have made major inroads into managing active RA. DMARDs were initially given as monotherapies but in recent years there has been greater emphasis on using combinations of two or more DMARDs as this has been shown to be more effective in disease control [43].

Since the mid-1990's a new treatment approach has been developed – the use of targeted biological treatments. They are usually given in combination with methotrexate or other DMARDs. Biologics have revolutionised the treatment of severe RA where they appear highly effective. A major limiting factor is their high cost [44].

Reducing disease activity appears a clear-cut well-defined goal. However, the degree of reduction required for a good ultimate outcome is not yet known. The enthusiasm for intensive treatment aimed at inducing remission [45] appears an inevitable next step. However, it is not clear whether this is appropriate for every patient. Furthermore, there remains uncertainty about the appropriate definition of remission in RA [46].

7.2 Synopsis of Specific Drug Treatment

7.2.1 Conventional Disease Modifying Anti-Rheumatic Drugs (DMARDs)

DMARDs are a diverse range of drugs [47]. They form a single group because they both improve symptoms and also, to a greater or lesser extent, modify the course of the disease. This means they reduce the progression of erosive joint damage and decrease disability [48, 49].

Many drugs have some features of DMARDs, but only a few have been accepted into clinical practice. The use of DMARDs varies with a small number being particularly favoured. The current situation is summarised in Table 1. At present methotrexate is the dominant DMARD because of its greater efficacy and retention compared to other DMARDs [50]. As the most widely used DMARD, methotrexate is now considered by regulatory agencies as a benchmark against which new agents must be tested. The majority of RA patients treated with DMARDs in most UK specialist units are either currently taking or have previously received methotrexate. Sulfasalazine, leflunomide and hydroxychloroquine (the latter largely as part of a combination regime), are the only other DMARDs used to any appreciable extent in the UK [51]. Other DMARDs are summarised in Table 1.

The efficacy of DMARDs involves reduced features of joint inflammation, such as fewer swollen joints and a lower ESR, a reduction in the progression of joint damage, particularly erosive damage, decreased levels of disability and improved quality of life. The harms, or adverse events, related to DMARDs include common problems seen with most DMARDs like low white cell or platelet counts and unique toxicities with specific DMARDs. There is a reasonable evidence base for their use as monotherapies [52-58]

7.2.2 Steroids

The commonest use of steroids in RA is as adjunctive agents to control disease flares; they may be given intra-articularly, intra-muscularly or orally. Since, in early disease, it has been suggested that steroids exert a disease-modifying effect, they form an initial but temporary component of several early arthritis combination regimens. They are also widely used as part of intensive DMARD combination therapy regimes in patients with uncontrolled established disease. There is a reasonably strong evidence base for their use [59-61].

7.2.3 DMARD Combinations With And Without Steroids

DMARDs can be used in combination (Table 1). This approach, initially advocated by McCarthy [62], has been examined in many clinical trials. Initial studies evaluated combinations which turned out to have excessive toxicity (gold-hydroxychloroquine) [63] or limited efficacy (methotrexate-azathioprine) [64]. This toxicity led early reviews to suggest risk/benefit ratios were unfavourable compared to monotherapy [65].

However, the situation changed when randomised controlled trials of methotrexate-ciclosporin [66], methotrexate-sulfasalazine-hydroxychloroquine [67] and methotrexate-sulfasalazine-steroids [68] reported improved disease control with mild or no excess toxicity in active RA; similar results were obtained in subsequent combination therapy studies. Combination DMARDs may not be required for all RA patients. In the only randomised trial of mild early RA patients on stable DMARD monotherapy they did not add benefit [69].

Overall, from our 2005 systematic review [70], and as suggested by a gradual expansion of its use in routine practice [71], the benefits of combination therapy are now thought to outweigh the risks in patients with active disease not controlled by monotherapy. They are also recommended in UK national guidelines for early RA patients with active disease to avoid delay in bringing the disease under control which is known to be associated with a poor outcome [72].

The randomised controlled trial evidence for using DMARD combinations is of crucial importance to the TACIT trial. It is summarised in detail for both early and established RA in two systematic reviews in the results section.

Table 1. **Disease Modifying Anti-Rheumatic Drugs (DMARDs)**

Range Of DMARDs			
Commonly used	Methotrexate	Leflunomide	Sulfasalazine
Infrequently Used	Hydroxychloroquine/Chloroquine	Injectable gold	Azathioprine
Rarely Used	Ciclosporin	Auranofin	Cyclophosphamide
Combinations Of DMARDs			
Methotrexate-based	Methotrexate, Sulfasalazine, Hydroxychloroquine Methotrexate, Leflunomide Methotrexate, Ciclosporin Methotrexate, Gold Methotrexate, Sulfasalazine Methotrexate, Azathioprine		
Other-DMARDs	Leflunomide, Sulfasalazine Gold, Hydroxychloroquine		
Steroid Based	Steroids, Methotrexate, Sulfasalazine Steroids, Methotrexate, Ciclosporin Steroids, Methotrexate		

7.2.4 Tumour Necrosis Factor Inhibitors (TNFis)

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 in the lymphoid system and joints and in less well-studied systems such as the central nervous system [73].

The proof of principle for inhibiting this cytokine came from an open label clinical study in which patients with RA received a single infusion of a TNFi. This showed a rapid response, including an early fall in C-reactive protein levels. However, the anti-inflammatory effect lasted only 6−12 weeks and was followed by a return of active disease [74]. As a result patients were retreated with further infusions; these showed responses of similar magnitude and duration [75]. The scene was set for a major clinical development programme.

There are currently five TNFis available to treat inflammatory arthropathies, summarised in Table 2. All have been shown to be effective in large clinical trials which have been collated in systematic reviews [76-80]. These can be subdivided into first generation agents (comprising etanercept, infliximab and adalimumab) and second generation agents (comprising certolizumab and golimumab). In RA all these agents are licensed for use in routine clinical care; they are also approved by NICE for use in the NHS although in some cases this has required a financial risk sharing agreement [81-83].

There is no clear-cut evidence that one of these agents is superior to another, and practical issues, including cost, determine which is chosen. There have been network meta-analyses of the efficacy and toxicities of different TNFis and these suggest potential minor differences in efficacy and adverse event risks [84-86].

Table 2. Tumour Necrosis Factors (TNFis)

TNFi	Site of Action	Dosing	Methotrexate
Infliximab	Binds soluble/transmembrane TNF-α and inhibits binding TNF-α to receptors	IV administration every 4-8 weeks	Essential to co-prescribe
Etanercept	Binds TNF-α and lymphotoxin and competitive inhibitor of TNF receptor	Subcutaneous twice weekly	Optional to co-prescribe
Adalimumab	Binds soluble/transmembrane TNF-α and inhibits binding TNF-α to receptors	Subcutaneous fortnightly	Optional to co-prescribe
Certolizumab	Binds soluble/transmembrane TNF-α and inhibits binding TNF-α to receptors	Subcutaneous fortnightly	Optional to co-prescribe
Golimumab	Binds soluble/transmembrane TNF-α and inhibits binding TNF-α to receptors	Subcutaneously monthly	Optional to co-prescribe

Infliximab must be given concurrently with methotrexate (or another DMARD in methotrexate intolerant patients) to prevent the formation of human anti-chimeric antibodies [87]. 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 especially in terms of the effect on bone erosion. Therefore all three drugs are almost always given with methotrexate or another DMARD [88].

The randomised controlled trial evidence for using TNFis in combination with methotrexate and other DMARDs is also of crucial importance to the TACIT trial. This evidence is also summarised in detail in the systematic reviews in Chapter 2.

The question of what to do when a TNFi failed was a crucial question, particularly in the early 2000s when other biologics were not available. There is only limited information about the relative merits of switching from one TNFi to another. The only randomised controlled trial studied golimumab in patients who had failed another TNFi; this showed some benefit from the switch [89]. The relative benefits of switching TNFis in patients who, for one reason or another, have not responded to their first biologic has also been addressed using observational data from registries and similar studies. Again, these studies provided some

evidence that switching TNFis can give clinically useful improvements though response rates for second and subsequent TNFis are lower than for first-time use [90].

More recently, several trials evaluating non-TNF targeted biologics including abatacept, rituximab and tocilizumab have provided convincing evidence that non-TNF biologics are effective in patients who have failed TNFi and this is increasingly the preferred approach [91, 92].

7.2.5 Other New Agents

A number of other biologics have been licensed, and in some cases approved by NICE, for treating RA. An early agent, anakinra, which is an interleukin 1 (IL1) receptor protein, is relatively ineffective [93] and is rarely used for treating RA. It is, however, highly effective in a range of other disorders including acute gout, some forms of juvenile arthritis and some familial periodic fevers. Further anti-IL1 agents are in late stage development, currently for these indications.

Rituximab targets B cells and is highly effective in active RA [94]. The exact mechanism of action is controversial as the presence of rheumatoid factor is not essential for its efficacy. Tocilizumab targets interleukin 6 and is also highly effective in active RA [95]. The third effective biologic, abatacept, targets costimulatory molecules on T lymphocytes [96].

Additionally, new non-biologic agents such as kinase inhibitors [97, 98] are also being introduced and one, tofacitinib, has already been licensed in the US [99]. Depending on their cost, these orally active agents may also change the treatment pathways for RA.

The role of these new agents in active RA and their optimal position in the treatment pathway is uncertain though, for historical reasons, they are generally used after TNF inhibitors. However, as they are not part of the TACIT trial, we have not considered the role of these treatments in detail.

7.3 Treatment Strategies

7.3.1 Supportive And Symptomatic Treatment

As with all long-term disorders the management of RA requires multiple inputs from a range of healthcare professionals from primary and secondary care. Patients need to be fully informed about their condition and able to access advice; this is one of the key roles for the specialist nurses. They need effective treatment for pain, using analgesics and non-steroidal anti-inflammatory drugs [100, 101], and their co-morbidities, notably ischaemic heart disease, need to be appropriately managed [102]. Finally they need access to physiotherapists and in some cases occupational therapists and they need to be encouraged to take regular exercise [103, 104]. The appropriate use of all these treatments is crucial to ensure good outcomes. However, they are outside the focus of the TACIT trial and so have not been considered in detail.

7.3.2 Treat To Target

There is evidence that intensive treatment is important in early RA both to suppress disease activity [105-109] and also to maintain low disease activity when it has been reduced. Welsing et al [110] investigated the longitudinal relationship between disease activity and radiological progression in two independent follow-up cohorts. Both showed significant relationships between disease activity and radiological progression, but only in patients seropositive for rheumatoid factor. The results support systematic monitoring to achieve persistent low disease activity. This approach, termed ‘tight control’ or “treat to target” includes several standard procedures such as:

a. A predefined treatment protocol to which treatments of individual patients are adjusted
b. Able to assess whether the treatment chosen is necessary and effective
c. Incorporates measures to ensure patients are not over-treated.

Many groups have reported on aspects of “tight control” [111-114]. Most used DAS or DAS28 to guide to treatment or as the primary end-point. Overall clinical and radiological outcomes were more favourable in patients receiving tight-control regimens In particular, remission rates were generally higher with tight control compared to conventional therapy. These improved clinical and radiological outcomes did not appear to be at the cost of increased drug toxicity.

7.3.3 Strategies For Dealing High Cost Agents: Access To TNFis And Other Biologics

The advent of high cost biologics necessitated new approaches as giving them to all RA patients is unaffordable. Different countries have taken divergent approaches to rationing these agents. Often such approaches are not so much evidence as consensus based. The TACIT trial is designed to examine new approaches to the optimal treatment pathways. This requires considering current modes of access to TNFis in the UK and elsewhere.

International groups, specialist societies and regulatory bodies recommend TNFis for patients with active RA who have failed to respond to conventional DMARDs [115-118]. Views differ on what constitutes active RA. The UK has used a disease activity score (DAS28) over 5.1 [115]. The concept of "failing DMARDs" is also controversial. In 2001 the National Institute For Health and Clinical Excellence (NICE) accepted the advice of the British Society for Rheumatology (BSR) that TNFis 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 [119]. These criteria, which are based on consensus expert opinion, have not subsequently changed, though the BSR have recommended reducing them to DAS28 >3.2 with at least three or more tender and three or more swollen joints [120].

There are major differences in the use of biologics for RA between European and North American Countries and differences in the clinical guidelines that are followed by rheumatologists when deciding to treat patients with these agents [121-124]. Most European countries have adopted EULAR recommendations and require DAS28 scores over 3.2. The UK is more restrictive in requiring the DAS28 to be over 5.1 [115]. There is some evidence that the use of biologics is lower than average in countries requiring higher DAS28 scores. Interestingly there are marked differences in biologics use across Europe; this ranges from under 10% of patients to over 30% with a mean of 19% [124]. Biologic use is influenced by several factors apart from guidelines for their access. Key factors include how biologics are distributed within the country (hospital distribution reduces prescribing), the relative wealth of the different countries in terms of their gross domestic product per capita (higher use in wealth countries) and the frequency of RA patients are treated with methotrexate (greater methotrexate use results in greater biologic prescribing).

Even in the UK with its tight restrictions on their use, 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). NICE currently estimate in the region of 35,000 patients with RA receive these treatments [125]. Costs will also increase as further non-TNFi biologics, such as rituximab, tocilizumab and abatacept, are more widely used for anti-TNF non-responders. Technical reasons mean that, though biosimilars are being introduced, they may remain relatively expensive unlike generic drugs.

7.3.4 Economic Modelling And Biological Treatments

Some studies and systematic reviews show that biologics are highly cost effective in RA. Other studies and systematic reviews show the opposite and suggest they fall substantially outside the conventional window for cost effectiveness. This paradox, which remains unresolved, is of crucial importance in determining whether biologics are used widely, and considered as early treatment choices, or if they should be treatments of last resort. The different findings reflect the use of different study designs and underlying assumptions, particularly about the progression of RA in patients who do not receive biologics.

Economic modelling conventionally extends beyond conventional randomised controlled trials [126], brings together cost and outcome evidence from a range of sources or provides indicative cost-effectiveness conclusions in the absence of relevant data from randomised controlled trials. For example, short-term trials do not often collect data about costs and health-related quality of life, do not involve all relevant head-to-head treatment comparisons, omit outcomes like employment, and are often not generalisable to other clinical settings. A variety of modelling methods are used including simple decision trees, Markov models and individual sampling models. Most economic studies in this area have evaluated the impact of biologics on quality-adjusted life years (QALYs); these reflect the years of perfect health added by the intervention. Biological treatments are compared to conventional treatments using incremental cost-effectiveness ratios (ICERs), which are the ratio between the difference in costs and the difference in benefits of two interventions. In the absence of direct QALY measures, values may be inferred from other available outcomes [127].

Recent systematic reviews of health economic studies in RA highlight the different conclusions based on assessments of the much the same set of published evidence. Schoels et al [128] identified 21 relevant studies of biologics and, based on society's willingness to pay ICER thresholds of US$50,000–100,000; they concluded combinations of TNFis with methotrexate were cost effective after conventional DMARD failure. The sequential use of TNF inhibitors has been a difficult problem to resolve; however, one study by Brennan et al reported favourable ICERs for using second TNF inhibitors as a class when compared to DMARD treatment [129]. An entirely different perspective was taken in a systematic review by van der Velde et al [130]. The identified 18 economic evaluations of biologic monotherapies/combination therapies compared to DMARDs and compared published ICERs for biologics in early RA and in methotrexate failures compared to continuing with methotrexate or trying an alternative biologic. They concluded that the economic evidence suggests biologics are not cost effective compared to DMARDs for RA in adults at a cost-effectiveness threshold of $50,000 (Canadian dollars) per QALY. They found mixed evidence of cost-effectiveness in selected populations at a willingness to pay threshold of $100,000 (Canadian dollars) per QALY. There is no simple way of resolving these different interpretations of apparently similar data. It is likely that small differences in study selection and data analysis can result in substantial variations in the findings. More work is needed to resolve this paradox.

8 STUDY OBJECTIVES

TACIT was designed to test the hypothesis that "patients with active RA who meet the NICE criteria for treatment with TNFis will gain equivalent benefit over 12 months at substantially less expense and without increased toxicity from starting treatment with intensive combination therapy with DMARDs".

9 INVESTIGATIONAL PLAN

9.1 Overall Study Design and Plan-Description

TACIT was an open-label, pragmatic, randomised, multicentre, two-arm trial. Patients were allocated to each arm in equal numbers. TACIT had a duration of 12 months.TACIT compared intensive combination DMARDs (cDMARDs) with TNFis given together with methotrexate or another DMARD in active established RA. Patients who failed to respond to cDMARDs were eligible to receive TNF-inhibitors after 6 months; this period was considered optimal to judge responsiveness to DMARDs.

Patients in the TNF inhibitor arm were assessed for response to their first TNF inhibitor at 6 months reflecting NICE guidance; those who do not respond tried another TNF inhibitor. If they failed they were offered alternative treatments like combination DMARDs.

9.2 Discussion of Study Design, including the Choice of Control Groups

TACIT focuses on the treatment of patients with active RA who have failed two DMARDs and meet the current NICE criteria for starting TNFis. These NICE criteria are based partly on evidence from randomised controlled trials, partly on economic modelling and partly on expert opinion. Our alternative view is that many of these patients will do equally well on intensive combination therapy with conventional DMARDs.

Agreeing the research hypothesis and designing a randomised controlled trial to test the hypothesis required considering the following three crucial issues:

1. The key outcome
2. The duration of the trial
3. Minimising the risk that patients randomised to receive combination DMARDs are not disadvantaged.

Our previous research has shown that HAQ is a sensitive patient-assessed outcome measure in active RA trials of DMARDs [131, 132]. It also has a crucial role in the economic modelling that is used to justify prescribing biologic treatments. HAQ had also been the primary outcome in the BeSt trial [133], the only previous trial involving comparisons between combination DMARDs and biologics published before TACIT started, albeit in early RA. We therefore decided changes in HAQ should the primary outcome measure.

The trial duration was more straightforward. Six months is probably too short a period of time to judge both clinical and cost-effectiveness. Longer than 12 months appeared to be

impractical and had no obvious advantage. As a consequence we decided that 12 months was the optimal time. This was also the duration at which the BeSt trial was first analysed [133].

The final issue, about minimising risks to patients randomised to combination DMARDs was more complex. There were two potential risks. The first was that they may have excessive toxicity. This risk would be minimised by independent oversight of the trial by the Data Monitoring and Ethics Committee. The other risk was inefficacy. We considered that if patients showed no response to combination DMARDs after 6 months treatment they should then be offered TNFis. We also considered that a response should adopt the same criteria that NICE recommend for maintaining patients on TNFis – a change in DAS28 score of 1.20 or more.

The final issue for TACIT is whether it could be a placebo-controlled trial or an open-label strategy trial. As combination DMARDs need to be individualised it would be impractical to deliver a placebo-controlled trial; instead we considered the trial had to be open label.

TACIT raised a number of ethical issues related to whether or not patients were being potentially denied access to highly effective treatments. These are considered in detail in the discussion.

9.3 Selection of Study Population

9.3.1 Inclusion Criteria

1. Males and Females aged over 18 years
2. Established RA by the 1987 criteria of the American College of Rheumatology [5]
3. Disease duration of at least 12 months
4. Meet NICE criteria for being prescribed TNF inhibitors [81]
    a. Disease Activity Score for 28 joints (DAS28) over 5.1
    b. Failure to respond to two disease modifying anti-rheumatic drugs (DMARDs) including methotrexate
    c. No contra-indications to TNF inhibitors (including possibility of pregnancy).

9.3.2 Exclusion Criteria

1. Unable or unwilling to give informed consent
2. Failure of, or contra-indications to, all proposed DMARD combinations (including possibility of pregnancy)
3. Serious inter-current illness
4. Patients on high dose steroids (in excess of 10mg prednisolone or equivalent per day at trial entry)

9.33 Removal of patients from therapy or assessment

There were no predetermined reasons for removal of patients from therapy or assessment.

9.4 Treatments

9.4.1 Treatments Administered

TACIT compared two treatment algorithms, (a) for TNF inhibitors and (b) for combination DMARDS. Treatments were individualised and depended on patients' responses.

9.4.1.1 TNF Inhibitors

The 3 licensed agents available when the trial started- adalimumab, etanercept, and infliximab –were allowed at standard doses (British National Formulary). The choice of TNF inhibitor reflected patient's preferences and local circumstances. Methotrexate was also given to maximise efficacy and (in the case of infliximab) reduce anti-chimeric antibodies. Patients intolerant to methotrexate took another DMARD. DAS28 scores at 3 and 6 months defined responses to therapy.

9.4.1.1.1 Patients had their TNFi stopped for one or more of three reasons

1. Lack of effect as defined by NICE criteria ie change in DAS28 <1.2 at 3 or 6 months
2. An adverse event which, in the opinion of the supervising specialist, necessitated treatment withdrawal
3. Patients could stop therapy for any reason should they wish (reasons to be specified if patient willing)

Patients in whom one TNFi was stopped were able to start another. This option represented current UK practice when the trial started. Patients who failed two TNFis for whatever reason were not able to start a third agent and required alternative treatments such as combination DMARDs. The principles of the treatment algorithm were as follows:

a. Starting a TNF inhibitor of choice on the basis of local circumstances and patients preferences
b. Assessed at 3 months: no change if good response (≥1.2 fall in DAS28); changed to second TNFi if <1.2 fall in DAS28
c. Assessed at 6 months: no change if good response (≥1.2 fall in DAS28); changed to second TNFi if <1.2 fall in DAS28; if two biologics already given and DAS28 change <1.2 TNF inhibitor stopped and patient offered DMARD combination or other therapy.

9.4.1.2 Combination DMARDs

Those with proven efficacy over DMARD monotherapy in randomised controlled trials were used including:

1. Triple therapy with methotrexate (methotrexate-sulfasalazine-hydroxychloroquine)
2. Other methotrexate combinations (methotrexate-ciclosporin, methotrexate-leflunomide and methotrexate-gold)
3. One sulfasalazine combination (sulfasalazine-leflunomide)
4. Additional monthly steroids (IM depomedrone (120mg stat) or equivalent) were used if needed.

DMARD combinations were stopped 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 DAS28 <1.2) which is similar to that with a TNF inhibitor but was only be implemented at 6 months.

The principles of the treatment algorithm comprised the following:

a. Initially: maximising initial DMARD/optimise administration (eg parenteral methotrexate); start second/third DMARD; (c) give IM depomedrone (whenever possible)
b. Second step: maximising dose of second/third DMARD
c. Third step; change combination (repeated if needed)
d. Additional option: continue IM depomedrone monthly short-term if RA remains active
e. Assess monthly and change treatment if change in DAS28 <1.2 or DAS28 >3.2
f. At 6 months start a TNF inhibitor if change in DAS28 <1.2
g. The target doses of different DMARDs used in combinations was as follows:
h. Methotrexate: 25mg weekly – preferably by IM injections though could be oral (achieved by 5mg increments)

i. Sulfasalazine: 3gm daily (starting at 500mg daily and increasing by 500mg increments)
j. Hydroxychloroquine: 400mg (starting at 200mg and increasing as one increment)
k. Ciclosporin: 3.5mg/kg (starting at 2mg/kg and increasing incrementally depending on creatinine levels)
l. Leflunomide: 20mg/day (staring at 10mg/day and not increasing if used in combination with methotrexate)
m. Gold: 20mg/month (starting with test dose, then 50mg/week for 20 weeks, then 50mg/month)
n. IM depomedrone given as 120mg/month for 3 months; further courses were given if the RA was still active.

Dose adjustments to all drugs depended on both disease activity and evidence of adverse events. Decisions about changes in treatment were made by the supervising rheumatologist, but were reviewed by the principal investigator (D Scott) or deputy to ensure the algorithm is followed.

9.4.1.3 Safety Monitoring

This followed national guidelines with monthly blood counts and liver function tests plus renal function (creatinine), urinalysis and blood pressure recording for some DMARDs [131, 132]. Patients were screened for tuberculosis.

9.4.2 Identity of investigational product

Tumour necrosis factor inhibitors drugs (adalimumab, etanercept, and infliximab) and combining two or more conventional disease modifying drugs (methotrexate, sulfasalazine, hydroxychloroquine, leflunomide, ciclosporin, azathioprine, penicillamine and gold injections (sodium aurothiomalate).

9.4.3 Method of assigning patients to treatment groups

Patients were randomly allocated to either the cDMARDs or TNFi group. The allocation sequence for randomisation was generated by the EDC system. Block randomisation was used in blocks of four with allocation balancing. Randomisation was stratified by region. Once a randomisation number was allocated the EDC system automatically informed the researcher at the individual centre and the trial co-ordinator by email. The trial co-ordinator informed the Pharmacy at site of the randomisation.

9.4.4 Selection of doses in the study

9.4.4.1 TNFi standard doses used in the study

a. Adalimumab (25 mg twice weekly or 50 mg once weekly)
b. Etanercept (40 mg on alternate weeks (i.e. 40mg every 2 weeks)
c. Infliximab (3 mg/kg, repeated 2 weeks and 6 weeks after initial infusion, then every 8 weeks; if response inadequate after 12 weeks, dose may be increased in steps of 1.5 mg/kg every 8 weeks, up to max. 7.5 mg/kg every 8 weeks; alternatively, 3 mg/kg may be given every 4 weeks; discontinue if no response by 12 weeks of initial infusion or after dose adjustment)

9.4.4.2 Combinations DMARDs used

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

9.4.5 Selection and timing of dose for each patient

The dose was administrated or taken at each visit at the same time.

9.4.6 Blinding

TACIT was not blinded and both clinicians and patients knew to which treatment strategy they had been allocated. The trial was un-blinded because individually optimised intensive cDMARD therapy cannot be given blindly. Many previous randomised controlled trials in RA using such treatments have been un-blinded. This approach provided the closest possible approximation to routine clinical care. The disadvantage of unblinded studies - that clinicians

have excessive influence on the results – was ameliorated because the primary outcome measure, HAQ was a patient self-completed questionnaire. In addition, another key outcome measure, x-ray changes were read without knowledge of treatment groups.

9.4.7 Prior and concomitant therapy

Non-opiate analgesics and non-steroidal anti-inflammatory drug were used as needed at standard doses. Patients taking methotrexate had folic acid (5mg/wk) to limit adverse events. Patients taking steroids had bone protection (eg alendronate and calcium/vitamin D). Other drugs (eg anti-hypertensives) were used as needed. Patients taking oral prednisolone up to 10mg at entry stayed on treatment. Intra-articular steroids were used as required.

9.4.8 Treatment compliance

Patients were asked if they have taken their medication at each visit.

9.5 Efficacy and Safety Variables

9.5.1 Efficacy and safety measurements assessed and flow chart

Formal outcome assessments was taken by the study metrologists at baseline, 6 and 12 months for primary outcome measures and 3 secondary measures but for DAS28 the measurements were done monthly.

9.5.2 Appropriateness of measurements

Table 3: Schedule assessment for primary and secondary outcome measures

	Screening	Baseline	6 months	12 months
Informed consent	x			
Medical history	x			
Effectiveness (primary and secondary variables)				
Function assessed using the Health Assessment Questionnaire (HAQ)		x	x	x
Swollen joint count (based on 66 joint counts)*		x	x	x
Tender joint count (based on 66 joint counts)*		x	x	x
Pain score (100mm Visual Analogue Score)*		x	x	x
DAS28*		x	x	x
Larsen score- X-rays		x	x	x
CSRI#		x	x	x
EQ5D		x	x	x
Quality of life assessed by the SF-36		x	x	x
Safety:				
Adverse events¥		x	x	x
Lab test:				
ESR*		x	x	x

*Also assessed at each month; #Data also obtained 3 months prior to baseline; ¥assessed at each interim visit

9.5.3 Primary efficacy variable(s)

The TACIT trial had the following outcome measures:

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

9.5.4 Drug concentration measurements

No drug concentration measurements were made for this trial

9.6 Data Quality Assurance

Data verification, consistency and range checks were performed prior to and at data entry by the Trial Co-ordinator and Data Manager at CTU with the EDC system. Additional range, consistency and missing data checks were performed, as appropriate, when the analysis was performed. All variables were examined for unusual, outlying, unlabelled or inconsistent values.

9.7 Statistical Methods Planned in the Protocol and Determination of Sample Size

9.7.1 Statistical and analytical plans (Appendix 16.5)

9.7.1.1 Recruitment And Follow-Up Patterns

Recruitment was recorded by year and region. The numbers of CRFs completed – excluding patients who had been withdrawn from therapy and were unwilling to continue follow up – were reported by treatment arms. The numbers of patients who have been withdrawn from therapy, lost to follow-up, or died while on study were also reported by treatment arms.

9.7.1.2 Baseline Comparability

Baseline characteristics were summarised by randomised group. Summary measures for the baseline characteristics of each group have been presented as mean and standard deviation for continuous (approximate) normally distributed variables, medians and interquartile ranges for non-normally distributed variables, and frequencies and percentages for categorical variables.

9.7.1.3 Intention To Treat Population

Except for enrolled patients who withdrew consent or were found to be ineligible at baseline visit and so never received any treatment, and for whom no data was therefore available,

analyses on an intention-to-treat (ITT) basis reflect the randomisation process. We also carried out two additional analyses populations:

a. A complete case population: these were observations that subjects completed without missing data or violation of the protocol and therefore referred to as `complete case analysis` throughout this report
b. A per protocol population: these were observations that excluded those patients who were found to deviate from the protocol (see section 4 in the statistical analysis plan for more details).

The results of the per protocol population were similar to that of the ITT population. Therefore the results from the ITT and complete case populations have been presented in the report.

9.7.1.4 Imputing Missing Data

All participants had observations at baseline. However, some subjects had missing data on the outcome variables at 6, 12 months or both. The outcome variables that had measurement at baseline, 6 and 12 months (HAQ, SF-36, EQ5D and Larsen score) were imputed under different assumption than DAS28 and its components, because DAS28 had monthly measurements.

All missing data was imputed regardless of the reason or reasons it was missing. For the subjects who had missing outcomes, the baseline outcomes and other explanatory covariates (treatment group, sex, age, ethnicity, region and disease duration) were used to impute the missing data, assuming unobserved measurements were missing at random.

For the subjects who had missing outcomes at 6 months, under the monotone assumption, baseline outcomes and explanatory covariates was used to impute the missing values at 6 months. Then, for those patients who had missing outcomes at 12 months, baseline and 6 months outcomes with explanatory covariates were used to impute the missing values at 12 months. If the outcome variables were missing at 6 and 12 months then the outcome variables at 6 months was imputed first followed by the outcomes at 12 months.

DAS28 and its component were imputed using multivariate sequential imputation using chained equations. Firstly, all missing values are filled in by simple random sampling with

replacement from the observed values. The first variable with missing values, say DAS28 at month one, was regressed on all other variables DAS28-0, DAS28-2,……..DAS28-12, restricted to individuals with the observed DAS28-1. Missing values in DAS28-1 were replaced by simulated data points drawn from the corresponding posterior predictive distribution of DAS28-1. Then, the next variable with missing was replaced by the same cycle [134].

The imputation was 20 cycles, where at the end of the cycle one imputed dataset was created and the process was repeated to create 20 imputed datasets. The 20 datasets were combined using Rubin's rules [135-137], therefore, the estimates and standard errors presented here are the combined ones. As an additional check of the robustness of the analyses performed to the missing at random assumption we further analysed the individual HAQ, EQ5D, Larsen score and DAS28 and its components) using the linear increments method of Diggle et al [138, 139] to handle the missingness. As the results obtained using this approach were qualitatively the same as that of the multiple imputation approach adopted, we report only the findings from the standard multiple imputation analyses.

9.7.1.5 Adjustment For Design Factors

Randomisation was stratified by region and therefore analyses of outcomes in the univariate or multivariable analyses were adjusted for region.

9.7.1.6 Outcome Assessed Every Six Months

The primary outcome (HAQ) and three of the secondary outcomes (EQ5D, SF-36 summary scores and Larsen scores) were measured at baseline, 6 and 12 months. As there was not a significant number of zero values for HAQ and other outcomes during follow-up, a linear regression model was used to analyse the change of these outcomes at 6 and 12 months. Thus change was defined as either 12 or 6 month scores minus baseline scores. The unadjusted univariate analysis (Model One) was adjusted for region, in order to account for design effect. The adjusted multivariable model (Model Two) included gender, ethnicity, age, region, and disease duration and baseline covariate as explanatory variables. Interactions between treatment and gender were assessed in the adjusted model two using Wald tests. The gender-specific interactions were not significant (for all outcomes $P>0.70$). The treatment regression coefficient provided an estimate of the mean difference in HAQ, EQ5D, SF-36 domains and Larsen score.

For individual components of the SF36 we used generalised estimating equations (GEE) to estimate the effect of treatment including baseline values as a covariate in these outcomes. Working correlation matrices were unstructured, which was not unduly restrictive given that measurements were only taken at three time points. As the data were analysed longitudinally, time was included as a covariate in model one and two. A final model tested specifically for interactions, between treatment and gender, treatment and time using Wald tests. The gender-specific interactions were not significant (for all outcomes P>0.50 in the overall test of all interaction terms). However, the interaction term between time and treatment gave borderline significant for some SF-36 domains (Physical Functioning, General Health Perception). We therefore reported period-specific treatment effect for those variables that had significant interaction terms.

9.7.1.7 Outcome Assessed Every Month

DAS28 and its components were measured monthly and were therefore analysed separately. Changes in DAS28 and its components were analysed using GEE to estimate the effect of treatment including baseline values as a covariate. Working correlation matrices were auto regressive with lag one. In this analysis interactions between time and treatment and gender and treatment were also assessed and found to be non-significant. Treatment effects were examined as subanalyses in two periods (1-6 months and 7-12 months). The estimates were presented as mean treatment effects (beta coefficients) with 95% confidence intervals. The sandwich estimator of error was used with the aim of obtaining robust estimates of precision. Statistical significance was determined at the 5%-level using a 2-sided test throughout. These analyses were based on the assumption that patients stayed on their original randomised treatment arm and thus ignored subsequent treatment switches.

9.7.1.8 Exploratory Analyses

The patients randomised to start cDMARDs fell into two categories. The first was those patients who remained on cDMARDs throughout TACIT. The second was those patients who switched to a TNFi after 6 months or longer because they had not fully responded to cDMARDs. The outcomes of these two categories of patients have been compared in a series of exploratory analyses; recognising that these are non-randomised in their original treatment arm. These analysis were done in all populations (ITT, complete case, and per protocol).

Further analysis was carried out on patients with observed data only. The rationale for using observed data rather than imputed data was that to define a response category for the individual changes in Larsen scores, erosive progression and the frequency and persistence of clinical responses (decreases in DAS28 scores ≥1.2) and DAS28 scores ≤2.6 (indicative of remission) were suited to use an available observations. One additional analytical approach used in these analyses was the construction of Kaplan–Meier plots and a comparison of treatment curves using the log rank test.

9.7.1.9 Toxicity

Proportion of serious adverse events was compared across randomised groups using Fisher's exact test as appropriate.

9.7.1.10 Software Specification

All data management and analyses were done using Stata, version 12.0 (StataCorp, College Station, TX) and the R statistical package (R Development Core Team, 2008).

9.7.2 Economic Evaluation Methods

9.7.2.1 Costs

Unit costs were applied to resource use data to calculate costs per participant. Unit cost estimates, their sources and any assumptions made for their estimation are detailed in Appendix 1, Tables 1 and Table 2. Medication unit costs were converted into cost per milligram (mg) based on the most cost efficient pack size, choosing maintenance prices over initial treatment prices and generic prices over branded ones to obtain conservative estimates.

Total costs were computed for each participant at each assessment point from two perspectives: health and social care; and societal. Health and social care costs included: inpatient services, outpatient services, primary care services, other community-based services, social services, trial medications and other prescribed medications. Two sets of societal costs were calculated, one which included health and social care costs plus participant lost productivity due to absence from work and one which included health and social care costs, participant lost productivity due to absence from work and, additionally, the cost of social security benefit payments received.

For the economic evaluation, costs generated from the 3-month CSRI data were extrapolated (multiplied by two) to cover the full 6 months prior to each follow-up point. All costs are reported in pounds sterling at 2010/11 prices. Discounting was not necessary as all costs were related to a 1-year period.

9.7.2.2 Outcome Measures

Cost-effectiveness analyses were based on the primary outcome measure, HAQ. Cost-utility analyses were based on QALYs derived from both the SF-36 and the EQ-5D. Utility weights appropriate to each measure were attached to health states at baseline, 6 and 12 months [140, 141]. QALY gains between baseline and 6 months, and between 6 months and 12 months were then calculated using the total area under the curve approach with linear interpolation between assessment points (and baseline adjustment for comparisons [142];).

9.7.2.3 Analyses, Missing Data And Sensitivity Analyses

Data were analysed using Statistical Product and Service Solutions (SPSS) for windows (version 20; IBM. 2011) [143] and Stata (version 11) [144] Participants were analysed according to the group to which they were randomised regardless of intervention compliance.

Costs and outcomes were compared at 6 and 12 months and are presented as means and standard deviations. Mean differences and 95% CIs were obtained by non-parametric bootstrap regressions (1000 repetitions) to account for the non-normal distribution commonly found in economic data, with adjustment for region as this was a stratification factor in the randomisation process. Although this was an RCT and participants in all groups were expected to be balanced at baseline, baseline costs and outcomes could be predictors of follow-up costs. To provide more relevant treatment-effect estimates [145], regressions to calculate mean differences in costs at follow-up included covariates for baseline cost from the same cost perspective, baseline HAQ, duration of illness, age, gender, region and ethnicity. Similarly, outcome comparisons (for the economic evaluation) at follow-up included covariates for baseline values of the same outcome plus baseline HAQ, duration of illness, age, gender, region and ethnicity.

Data were entered via an electronic data capture system using MedSciNet Database which was programmed to disallow individual item non-response on the CSRI service use section. There was thus no item non-response for this part of the CSRI. For lost employment data, if

the CSRI indicated this was positive, but the amount was missing, the mean lost employment cost for that arm at that time point (only for those who had lost employment and had valid data) was substituted. For social security benefit data, if the CSRI indicated this was positive, but the amount was missing, then unit costs for specified benefits were applied. Where receipt of benefits was positive but specific benefits were unspecified, the mean benefit cost for that arm at that time point (only for those who received benefits and had valid data) was substituted. For non-trial medication data, if the medication name was missing, but other information (e.g. dose) indicated some use, an average prescription cost (from Department of Health prescription cost analyses) was assumed. If a medication name was provided but usage quantity was missing, an average prescription cost for that particular medication was assumed.

Analyses were based on available cases for each analysis i.e. excluded non-responders to the CSRI, HAQ, EQ5D or SF-36 at each time point if there were any. To explore the potential impact of excluding non-responders in this available case approach, we examined sociodemographic and clinical characteristics of those included in the analyses and those in the full sample. We also carried out an intention to treat analysis, imputing missing 6 and 12 month total costs and outcomes using the multiple imputation command in Stata (version 11). Imputations of missing 6 and 12 month costs were based on variables expected to predict follow-up costs: baseline HAQ, duration of illness, age, gender, region, ethnicity, trial arm and equivalent baseline cost (and equivalent cost at 6 months for 12 month imputations). Imputations of HAQ scores at 6 and 12 months were based on baseline HAQ, duration of illness, age, gender, region, ethnicity and trial arm (and HAQ at 6 months for 12 month imputations). Imputations of missing QALYs at 6 and 12 months were based on baseline HAQ, duration of illness, age, gender, region, ethnicity, trial arm and equivalent baseline utility score (and utility score at 6 months for 12 month imputations). Cost and outcome data for the resulting imputed full sample were analysed and presented as per the base (available) case data.

9.7.2.4 Cost-Effectiveness And Cost-Utility Analyses

Accounting for the three cost perspectives and three outcomes, there were nine possible cost-outcome combinations to consider in the economic evaluation. Incremental cost-effectiveness ratios (ICERs) were calculated for any combination which showed both significantly higher costs and better outcomes in either the intervention group or control group.

Uncertainty around cost-effectiveness/cost-utility was explored using cost-effectiveness acceptability curves (CEACs) based on the net-benefit approach [146]). These curves address some of the problems associated with examining ICERs and show the probability that one intervention is cost-effective compared to the other, for a range of values that a decision maker would be willing to pay for an additional unit of each outcome (i.e. per additional QALY or per additional point improvement in HAQ). Net benefits for each participant were calculated using the following formula, where λ is the willingness to pay for one additional unit of outcome:

Net benefit = (λ x outcome) - cost.

A series of net benefits were calculated for each individual for λ values ranging between £0 and £50,000 per QALY gain and per point improvement on the HAQ. After calculating net benefits for each participant for each value of λ, coefficients of differences in net benefits between the trial arms were obtained through a series of bootstrapped linear regressions (1000 repetitions) of group upon net benefit which included the baseline value of the same cost category and the same outcome as covariates plus baseline HAQ, duration of illness, age, gender, region and ethnicity. The resulting coefficients were then examined to calculate for each value of λ the proportion of times that the cDMARDs group had a greater net benefit than the TNFi group. These proportions were then plotted to generate CEACs for all three outcomes from the health and social care perspective at 6 months and at 12 months.

9.7.3 Determination of sample size

TACIT sought 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 sample size was defined by the trial 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 TNFis.

The sample size calculation was based on changes in HAQ scores in:

1. The ATTRACT trial (Infliximab versus placebo in RA patients receiving concomitant methotrexate) 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 [147]
2. The CARDERA (Combination Anti-Rheumatic Drugs in Early Rheumatoid Arthritis) trial, an MRC funded UK trial of 464 patients 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 [148].
3. We took 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 was therefore designed under the assumption that cDMARDs and TNFis produce equivalent reductions in HAQ and that a difference of less than 0.22 would be regarded as equivalence.

Formally, the trial was 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 was required to achieve 90% power. To allow for a dropout of 5-7%, we planned to recruit 190 patients.

9.8 Changes in the Conduct of the Study or Planned Analyses

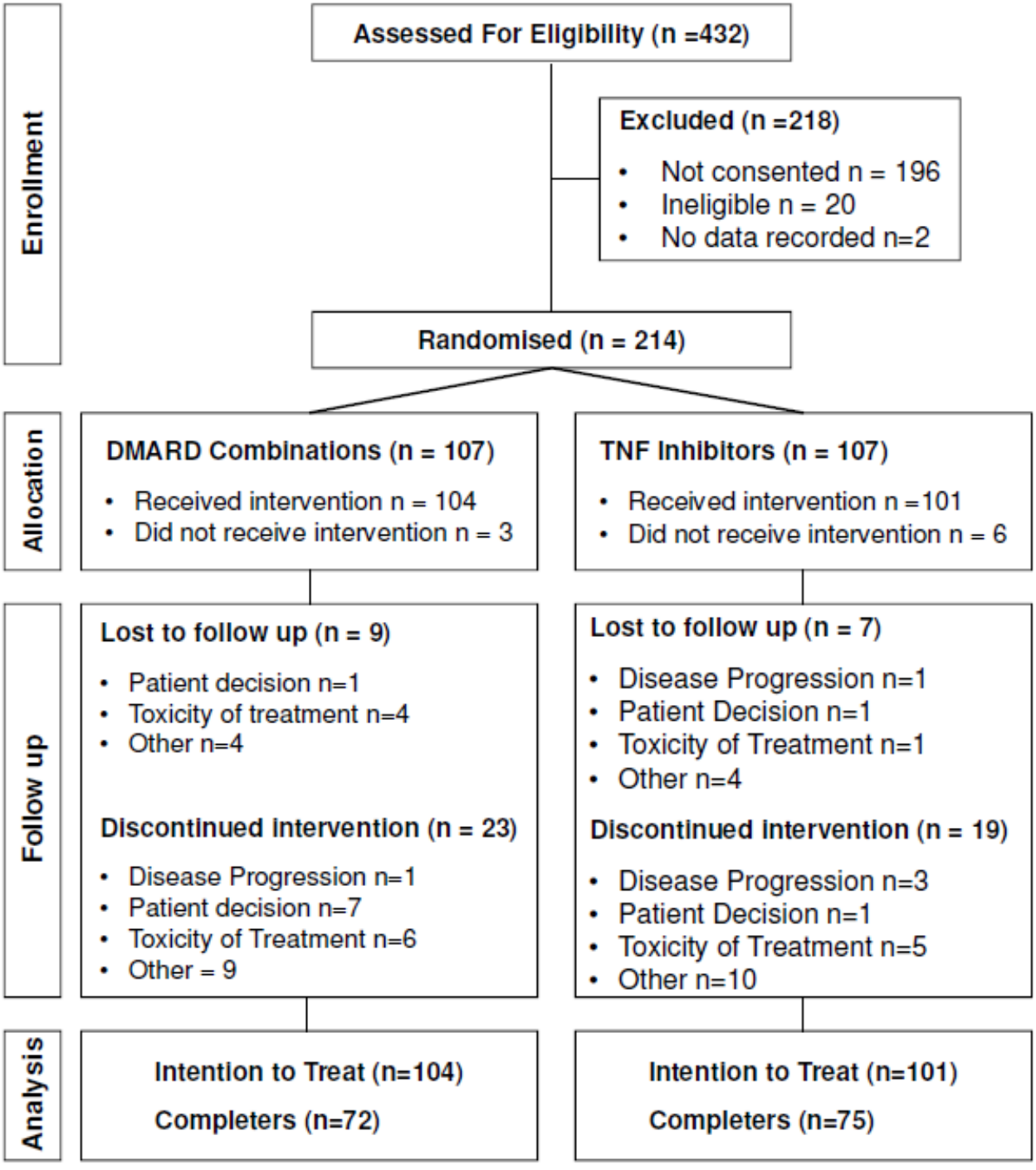
No changes were made to the statistical analysis plan.

10 STUDY PATIENTS

10.1 Disposition of Patients

TACIT screened 432 patients from 2008 to 2010 at 24 rheumatology clinics: 218 patients were excluded (196 did not consent): 214 were randomised. 9 randomised patients withdrew before being treated (6 decided not to participate). 104 started cDMARDs and 101 started TNFis.

Figure 1 CONSORT Diagram For TACIT Trial



10.2 Protocol Deviations

Through monitoring and final data cleaning in preparation for database lock, it was discovered that there had been several types of protocol violations among patients enrolled in the trial and still taking trial medication. Those protocol violations and affected patients were presented to the DMEC, and suggested areas for flexibility were proposed. The DMEC were willing to allow flexibility in certain areas, as summarised in the 'DMEC flexibility' column of Table 4 below.

For intention to treat analysis: all enrolled patients who subsequently received trial medication will be included into the analyses. However, the patients who have violated the protocol outside of the flexibilities agreed by the DMEC (deviation types 1 to 7) will be excluded from this analysis. See Figure 1 for those patients who withdrawn and lost to follow up for more details.

Table 4: Types of protocol deviations and permitted flexibilities

Deviation type number	Protocol deviation	Protocol Criteria	DMEC flexibility
1	Multiple DMARDS (whilst on TNF Inhibitor)	Patients randomised to the TNF inhibitor arm are permitted to take 1 DMARD only (Methotrexate unless contraindicated)	No flexibility
2	High dose steroids	Not on high dose steroids (in excess of 10mg prednisolone or equivalent per day at trial entry)	No flexibility
3	Trial medication given before baseline	Not expressly stated, but trial medication should commence immediately after the baseline outcome data are collected	No flexibility
4	Baseline outcome data (questionnaires) collected 3 months	Not expressly stated, but trial medication should commence immediately after the baseline	No flexibility

	after starting trial medication	outcome data are collected	
5	>8 weeks off 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	No flexibility
6	Ineligible - History of Serious Illness	No Serious Intercurrent Illness	No flexibility
7	Changed treatment at 6 months despite >1.2 improvement in DAS	At 6 months: no change in treatment if good response (≥1.2 fall in DAS)	No Flexibility
8	Steroid injections given between Screening and Baseline	If a steroid injection is given before baseline, the baseline assessment should be delayed for 1 month after the date of the injection.	Include in the ITT and the per protocol analysis, but screening assessment should be used as the baseline rather than the one immediately following the steroid injection
9	Milestone assessments performed outside visit window	Milestone assessments (6 and 12 months) must be performed within +/- **14** days of the estimated date of assessment;	Milestone assessments must be performed within +/- **31** days

		this was not defined in the protocol but as part of the TACIT Working Practice	of the estimated date of assessment
10	Insufficient medication at baseline	At Baseline, atients must be started on combination DMARDs if on the DMARD arm and a TNF-Inhibitor with accompanying DMARD if on the TNF-Inhibitor arm	Allow up to **1** month from baseline for the introduction of the second trial medication
11	Chest x-ray not taken prior to randomisation	Negative screen for tuberculosis (including chest X-ray)	Local methods can be used
12	Patient not switched at 6 months	Patients assessed at 6 months: no change if good response (≥1.2 fall in DAS); change treatment from **6** month assessment if <1.2 fall in DAS *(Change to 2nd TNF Inhibitor if on TNF Inhibitor arm, Change to 1st TNF Inhibitor if on Combination DMARD arm)*	Switch permitted at up to **9** months; however, the decision to switch is still based on the 6 month timepoint.

11.0 EFFICACY EVALUATION

11.1 Data Sets Analysed

Between September 2008 and December 2010 432 patients were screened, 214 randomised and 205 treated (Figure 1). 104 patients were randomised to cDMARDs and 101 to TINFis.

11.2 Demographic and Other Baseline Characteristics

Demographic and disease assessments in the 205 treated patients were similar in both groups (Table 5).

Table 5: Table Baseline Demographic And Clinical Characteristics

		cDMARDs (n=104)	**TNFis (n=101)**
Demographic Variables			
Mean Age (SD) in years		58 (13)	57 (11)
Gender	Female	73 (70%)	79 (78%)
	Male	31 (30%)	22 (22%)
Ethnic Group	White	89 (86%)	92 (91%)
	Black (African, Caribbean, Black Other)	6 (6%)	2 (2%)
	Asian (Bangladeshi/Indian, Pakistani)	8 (8%)	6 (6%)
	Other/Mixed Ethnic Group	1 (1%)	1 (1%)
Median Disease Duration (IQR) in years		4.4 (1.6-9.9)	5.9 (2.2-13.4)
Mean Height (SD) in metres		1.64 (0.11)	1.66 (0.09)
Mean Weight (SD) in kg		78 (20)	81 (17)
Median BMI (IQR) in kg/m^2		29 (24, 33)	29 (25, 32)
Clinical Variables			
Mean DAS28 Score (SD)		6.2 (0.9)	6.3 (0.8)
Mean Tender Joint Count (SD)		16 (7)	18 (7)
Mean Swallow Joint Count (SD)		11 (6)	11 (7)
Mean ESR (SD) in mm/h		33(26)	30 (23)
Mean Patient Global Visual Analogue Score (SD) in mm		68 (20)	68 (21)
Mean HAQ Score (SD)		1.8 (0.6)	1.9 (0.7)
Mean Larsen Score (SD)		45 (42)	38 (39)
Mean EQ5D Utility Score (SD)		0.39 (0.31)	0.35 (0.31)
Mean SF-36 PCS (SD)		28 (7)	27 (7)
Mean SF-36 MCS (SD)		43 (12)	41 (12)

SD= Standard Deviation; IQR= interquartile range

11.3 Measurements of Treatment Compliance

Follow-up data was shown in Figure one. 147/205 (72%) patients completed 12 months treatment, 16/205 (8%) were lost to follow up and 42/205 (20%) discontinued their intervention and were followed-up. 16/205 (8%) stopped treatment for toxicity (10 cDMARDs, 6 TNFis), 5/205 (2%) for disease progression (1 cDMARDs, 4 TNFis) and 31/205 (15%) for patients' decisions (15 cDMARDs, 16 TNFis). No concentration was measured in this trial.

11.4 Efficacy Results and Tabulations of Individual Patient Data

11.4.1 Analysis of efficacy

11.4.1.1 Disability, Quality Of Life And Erosive Damage (Assessed Every Six Months)

The outcome measures specifically collected every 6 months include the primary outcome, HAQ, and three secondary outcomes - EQ5D, SF-36 scores and Larsen scores for x-ray damage.

11.4.1.1.1 Changes in HAQ

A. In Intention To Treat Population

Initial HAQ scores were similar in patients randomised to receive cDMARDs (mean 1.80, 95%CI 1.68, 1.91) and TNFis (mean 1.90, 95% CI 1.77, 2.03). After 12 months HAQ scores had changed by a mean of 0.45 (95% CI 0.34, 0.55) in patients randomised to cDMARDs and by 0.30 (95% CI 0.19, 0.42) in patients randomised to TNFis (Table 6). The unadjusted and adjusted linear regression analyses (Table 8) showed patients randomised to start cDMARDs had a greater reduction in HAQ than those randomised to start TNFis. The unadjusted coefficient (adjusted for region only) was 0.14 (95% CI: -0.01, 0.29). After adjusting for demographic factors (age, gender, ethnicity, disease duration and region) and baseline scores the adjusted coefficient was 0.15 (-0.003, 0.31). The unadjusted linear regression analysis showed the reduction in HAQ was of borderline statistically significance in patients randomised to cDMARDs (p=0.075). After adjusting for demographic factors and baseline scores, the estimates showed a stronger statistically significant difference in the reduction in HAQ with cDMARDs (p=0.046) (Table 8). The minimally clinical detectable difference in HAQ is 0.22. The difference between 12-month HAQ scores in patients starting cDMARDs and TNFis was 0.15 and the 95% confidence intervals fell within 0.22 of this difference. TACIT therefore provides no evidence of a clinically important difference in 12-month HAQ

scores between groups. At 6 months HAQ scores decreased by a mean of 0.28 (95%CI 0.18, 0.38) in patients randomised to cDMARDs and by 0.35 (95% CI 0.23, 0.46) in patients randomised to TNFis (Table 6). This difference was not significant in either the unadjusted or in the adjusted model (Table 8). The overall pattern of change is shown in Figure 2.

58 of the 104 patients in the cDMARD group remained on cDMARDs and 46 switched to TNFis after 6 months. Over 12 months both sets of patients had similar changes in HAQ and there was no evidence of a difference between groups by linear regression analysis (Table 10 and Figure 3). Comparing changes in HAQ in both these groups by general estimating equations showed no evidence that there were any significant differences between the two sub-groups in both an unadjusted and an adjusted model (Table 11).

B. Complete Case Analysis

Initial HAQ and HAQ changes were similar in patients randomised to cDMARDs and TNFis. There was no evidence of a significant difference between groups (Appendix 2 Tables 1, 3 and Figure 1). However, in the longitudinal analysis (Appendix 2 Table 6) there was some evidence of treatment difference in unadjusted and adjusted model.

11.4.1.1.2 Changes in EQ5D

A. Intention To Treat Population

Initial EQ5D scores were similar in patients randomised to receive cDMARDs (mean 0.39, 95%CI 0.33, 0.45) and to receive TNFis (mean 0.35, 95% CI 0.28, 0.41). At 12 months EQ5D scores changed by a mean of -0.20 (95% CI -0.27, -0.13) in the patients randomised to cDMARDs and by -0.14 (95% CI -0.21,-0.08) in the patients randomized to TNFis (Table 6). There was no significant difference between groups in the unadjusted model (Table 8). The adjusted model, in which the coefficient was -0.11(95% CI -0.18,-0.03), showed a significant increase in the patients randomised to cDMARDs compared with TNFis (p=0.009). At 6 months EQ5D scores changed by a mean of -0.14 (95%CI -0.20, -0.08) in patients randomised to cDMARDs and by -0.17 (95% CI -0.23, -0.11) in patients randomised to TNFis (Table 6). The difference was not significantly between treatment groups in either the unadjusted or the adjusted models (Table 8). The overall pattern of change is shown in Figure 2.

Over 12 months both sets of patients had changes in EQ5D (Table 10 and Figure 3); in patients remaining on cDMARDs, EQ5D improved by a mean of -0.26 (95% CI -0.35, -0.17) and in patients switching to TNFis EQ5D improved by a mean of -0.13 (95% CI -0.24, -0.02). Comparing these changes in EQ5D over 12 months by linear regression (Table 10) showed the difference was of borderline significance (p=0.069).

B. Complete Case Analysis

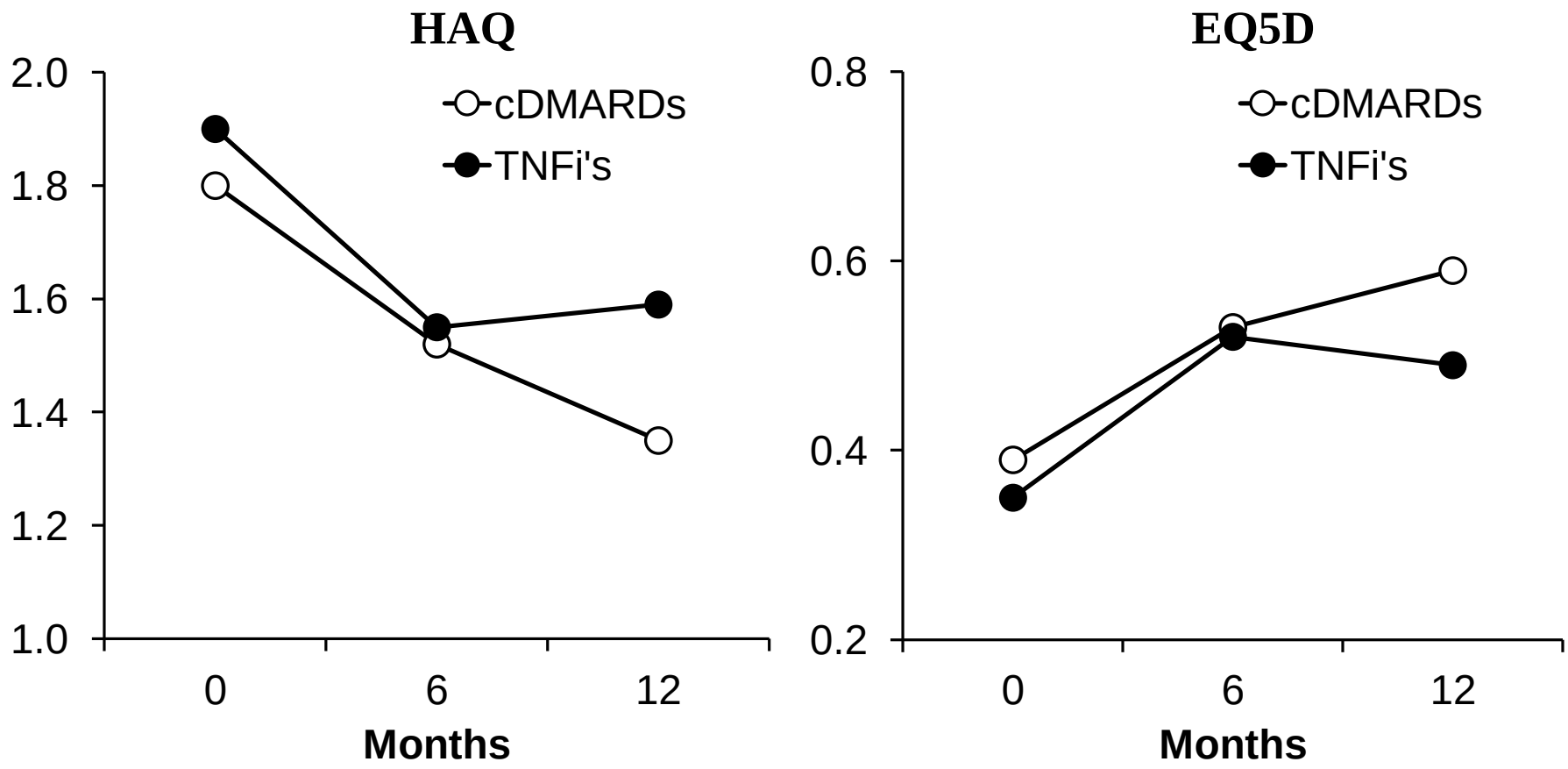
Initial EQ5D and EQ5D changes were similar in patients randomised to cDMARDs and TNFis. There was no evidence of a significant difference between groups (Appendix 2 Tables 1 and 4 and Figure 1).

Table 6: Primary Outcome And Other Key Secondary Outcomes In Intention To Treat Population

Individual Mean And 95% Confidence Intervals Scores Shown By Treatment Group

Measures	**Combination DMARD Group (N=104)**					**TNF Inhibitor Group (N=101)**				
	Initial	*6 months*	*12 months*	*Change 0-6*	*Change 0-12*	*Initial*	*6 months*	*12 months*	*Change 0-6*	*Change 0-12*
HAQ	1.80 [1.68, 1.91]	1.52 [1.39,1.65]	1.35 [1.20,1.50]	0.28 [0.18,0.38]	0.45 [0.34,0.55]	1.90 [1.77,2.03]	1.55 [1.39,1.71]	1.59 [1.43,1.76]	0.35 [0.23,0.46]	0.30 [0.19,0.42]
EQ5D	0.39 [0.33, 0.45]	0.53 [0.48,0.59]	0.59 [0.53,0.65]	-0.14 [-0.20,-0.08]	-0.20 [-0.27,-0.13]	0.35 [0.28,0.41]	0.52 [0.46,0.58]	0.49 [0.43,0.55]	-0.17 [-0.23,-0.11]	-0.14 [-0.21,-0.08]
Larsen score	45.1 [37.0, 53.2]	45.9 [37.7,54.0]	46.3 [38.1,54.5]	-0.78 [-1.65,-0.02]	-1.26 [-2.34,-0.19]	37.9 [30.2,45.6]	38.7 [30.81,46.6]	39.3 [31.2,47.4]	-0.81 [-1.65,0.02]	-1.37 [-2.48,-0.26]

Figure 2 Mean HAQ And EQ5D Scores In Intention To Treat Population



11.4.1.1.3 Changes in SF-36

A. Intention To Treat Population

Changes in the SF-36 profiles and physical component and mental component summary scores (PCS and MCS) are summarised in Table 7. There was a complex pattern of change. There were large mean changes (over 20) in the role physical domain at both 6 and 12 months in both groups. At 12 months physical functioning, pain, vitality, social functioning and role emotion showed changes between 10 and 20 in both groups. General health perception and mental health showed smaller changes over 12 months, below 10, in both groups. We have not undertaken an in-depth statistical analysis of changes in the individual domains. However, longitudinal analyses assessing changes in these SF36 domains at both 6 and 12 months (Table 9) mainly showed no significant differences between treatment groups in unadjusted models or in adjusted models.

Initial PCS scores were similar in the two groups: in patients randomised to cDMARDs the mean was 28.5 (95% CI 27.1, 29.7); in patients randomised to TNFis the mean was 27.3 (95% CI 25.9, 28.7). At 12 months PCS scores changed by a mean of -6.0 (95% CI -8.1,-3.8) in patients randomised to cDMARDs and by -5.8 (95% CI -7.9, -3.7,) in patients randomized to TNFis (Table 7). There was no significant difference between groups in the unadjusted or adjusted models on linear regression analysis (Table 8). At 6 months PCS scores changed by a mean of -4.2 (95%CI -6.22, -2.1) in patients randomised to cDMARDs and by -7.6 (95% CI -9.5, -5.8) in patients randomised to TNFis (Table 7). This difference was significant different (Table 8) on linear regression analysis in both the unadjusted model 2.66 (95% CI 1.50, 3.83; $p<0.001$) and in the adjusted model -1.75 (95% CI 0.64, 2.86; $p=0.002$).

Initial MCS scores were similar in the two groups: in patients randomised to cDMARDs the mean was 43.4 (95% CI 41.0, 45.8); in patients randomised to TNFis the mean was 40.7 (95% CI 38.3, 43.1). At 12 months MCS scores changed by a mean of -5.0 (95% CI -7.8, -2.2) in the patients randomised to cDMARDs and by -5.4 (95% CI -2.7, -8.2) in the patients randomized to TNFis (Table 7). There was no significant difference between groups in the unadjusted or adjusted model (Table 8). At 6 months MCS scores changed by a mean of -3.6 (95%CI -6.1, -1.1) in patients randomised to cDMARDs and by -4.3 (95% CI -7.2, -1.4) in patients randomised to TNFis (Table 7). There was no significant difference between treatment groups in the unadjusted or adjusted in linear regression analysis (Table 8).

B. Complete Case Analysis

Changes in SF-36 profiles and initial scores and changes in scores for the PCS and MCS were similar in patients randomised to cDMARDs and TNFis. There was no evidence of a significant difference between groups in the longitudinal analysis (Appendix 2 Tables 2 and 4).

Table 7: SF-36 Domains And Summary Scores In Intention To Treat Population

Individual Mean And 95% Confidence Intervals Scores Shown By Treatment Group

Domains	**Combination DMARDs (N=104)**					**TNF Inhibitors (N=101)**				
	Initial	*6 months*	*12 months*	*Change 0-6*	*Change 0-12*	*Initial*	*6 months*	*12 months*	*Change 0-6*	*Change 0-12*
Physical Function	30.1 [25.8, 34.5]	36.7 [31.3, 42.2]	42.1 [36.4, 47.7]	-6.58 [-12.2, -0.9]	-11.9 [-17.5, -6.3]	24.6 [20.5, 28.7]	40.0 [34.4, 45.5]	37.8 [31.9, 43.6]	-15.4 [-20.8, -10.1]	-13.2 [-18.9, -7.5]
Role physical	14.9 [9.1, 20.7]	36.2 [28.0, 44.3]	37.2 [28.2, 46.1]	-21.3 [-30.7, -11.8]	-22.3 [-31.9, -12.6]	12.4 [7.3, 17.5]	37.6 [29.2, 46.1]	33.1 [24.4, 41.8]	-25.2 [-33.6, -16.9]	-20.7 [-29.5, -11.9]
Pain	28.1 [25.0, 31.3]	41.2 [37.4, 45.1]	46.4 [41.5, 51.2]	-13.1 [-17.5, -8.7]	-18.2 [-23.5, -12.9]	26.3 [22.8, 29.8]	45.5 [40.9, 50.0]	44.7 [40.0, 49.4]	-19.2 [-24.1, -14.3]	-18.4 [-24.0, -12.9]
General Health Perception	35.8 [32.3, 39.3]	40.9 [37.1, 44.8]	44.6 [39.8, 49.4]	-5.2 [-9.3, -1.1]	-8.9 [-13.7, -4.1]	31.4 [28.1, 34.7]	44.1 [39.9, 48.3]	39.6 [35.3, 44.0]	-12.7 [-17.1, -8.3]	-8.2 [-12.8, -3.7]
Vitality	30.3 [26.2, 34.5]	36.8 [32.5, 41.2]	40.4 [35.3, 45.5]	-6.5 [-11.3, -1.7]	-10.1 [-14.9, -5.2]	26.6 [22.9, 30.3]	40.4 [35.9, 44.9]	40.1 [35.4, 44.8]	-13.8 [-18.4, -9.2]	-13.5 [-18.5, -8.4]
Social Functioning	50.2 [45.4, 55.1]	61.6 [56.4, 66.8]	66.2 [60.6, 71.8]	-11.4 [-16.6, -6.1]	-16.0 [-22.0, -9.9]	42.1 [37.1, 47.0]	58.9 [53.6, 64.3]	59.8 [54.0, 65.5]	-16.8 [-22.8, -10.9]	-17.7 [-24.2, -11.1]
Role Emotion	43.9 [35.2, 52.6]	58.3 [49.3, 67.3]	60.4 [50.8, 70.0]	-14.4 [-25.1, -3.6]	-16.5 [-28.0, -5.0]	35.3 [26.5, 44.1]	50.9 [41.7, 60.1]	52.1 [42.7, 61.5]	-15.6 [-26.8, -4.3]	-16.8 [-28.3, -5.3]
Mental Health	61.9 [58.0, 65.8]	68.1 [64.2, 72.0]	70.4 [66.3, 74.5]	-6.2 [-10.6, -1.8]	-8.5 [-13.3, -3.7]	58.8 [54.3, 63.3]	65.8 [61.4, 70.2]	67.8 [63.7, 71.9]	-7.0 [-12.4, -1.6]	-9.0 [-14.1, -4.0]
PCS	28.4 [27.1, 29.7]	32.6 [30.7, 34.4]	34.4 [32.2, 36.5]	-4.2 [-6.2, -2.1]	-6.0 [-8.1, -3.8]	27.3 [25.9, 28.7]	34.9 [32.9, 36.9]	33.0 [31.1, 35.0]	-7.6 [-9.5, -5.8]	-5.8 [-7.9, -3.7]
MCS	43.4	47.0	48.4	-3.6	-5.0	40.7	45.0	46.1	-4.3	-5.4

Domains	**Combination DMARDs (N=104)**					**TNF Inhibitors (N=101)**				
	Initial	*6 months*	*12 months*	*Change 0-6*	*Change 0-12*	*Initial*	*6 months*	*12 months*	*Change 0-6*	*Change 0-12*
	[41.0, 45.8]	[44.6, 49.4]	[46.0, 50.8]	[-6.1, -1.1]	[-7.8,-2.2]	[38.3, 43.1]	[42.4, 47.6]	[43.7, 48.6]	[-7.2, -1.4]	[-8.2, -2.7]

PCS = Physical component Summary score; MCS = Mental Component Summary score

Table 8: Linear Regression For Adjusted And Unadjusted Treatment Effects For Primary and Secondary Outcome Measures In Intention To Treat Population

Outcome		**Model 1 (Unadjusted) Treatment + Region**		**Model 2 (Adjusted) Treatment + Demographics + Baseline Score**	
		Coefficient (95% CI)	*p-value*	*Coefficient (95% CI)*	*p-value*
Change In HAQ	*12 months*	0.14 (-0.01, 0.29)	0.075	0.15 (0.00, 0.31)	0.047
	6 months	-0.07 (-0.22, 0.08)	0.360	-0.08 (-0.23, 0.07)	0.311
Change In EQ5D	*12 months*	-0.06 (-0.15, 0.04)	0.245	-0.11 (-0.18, -0.03)	0.009
	6 months	0.03 (-0.06, 0.11)	0.500	0.01 (-0.07, 0.08)	0.882
Change In Larsen score	*12 months*	0.11 (-1.45, 1.67)	0.891	0.35 (-1.37, 2.06)	0.689
	6 months	0.03 (-1.09, 1.15)	0.958	0.24 (-1.02, 1.51)	0.704
Change In SF-36 PCS	*12 months*	-0.23 (-3.26, 2.79)	0.880	-1.40 (-4.22, 1.41)	0.327
	6 months	2.66 (1.50, 3.83)	<0.001	1.75 (0.64, 2.86)	0.002
Change In SF-36 MCS	*12 months*	0.42 (-3.51, 4.35)	0.832	-1.73 (-5.07, 1.61)	0.307
	6 months	0.68 (-3.17, 4.54)	0.728	-1.62 (-4.94, 1.70)	0.336

Demographics adjusted for are age, gender, ethnicity, disease duration and region. Combination DMARDs was the reference group

Table 9: Longitudinal Analysis Comparing Effect Of Randomised Treatment Arm On Individual SF-36 Domains In Intention To Treat Population Using Generalised Estimating Equations

Variable		**Model 1 (Unadjusted) Treatment + Region**		**Model 2 (Adjusted) Treatment + Demographics + Baseline Score**	
		Coefficient (95% CI)	*p-value*	*Coefficient (95% CI)*	*p-value*
No Period Specific Treatment Effects					
	SF36 Role Physical	-0.77(-6.52, 4.97)	0.793	0.40(-4.74, 5.53)	0.879
	SF36 Pain	-1.50(-4.76, 1.76)	0.368	-0.21(-2.95, 2.53)	0.880
	SF36 Vitality	-2.92(-6.05, 0.21)	0.067	-1.76(-4.54, 1.02)	0.215
	SF36 Social Functioning	-1.81(-5.66, 2.03)	0.356	1.80(-1.43, 5.04)	0.274
	SF36 Role Emotion	-0.43(-7.64, 6.78)	0.907	3.98(-1.58, 9.54)	0.160
	SF36 Mental Health	-0.31(-3.46, 2.85)	0.848	1.35(-1.06, 3.76)	0.272
Period Specific Treatment Effects					
Period (1-6)	SF36 Physical Functioning	8.69(1.04, 16.34)	0.026	5.52(-1.74, 12.77)	0.136
	SF36 General Health Perception	7.37(1.43, 13.30)	0.015	4.20(-0.78, 9.18)	0.098
Period (7-12)	SF36 Physical Functioning	1.16(-6.49, 8.81)	0.767	-3.12(-10.44, 4.19)	0.403
	SF36 General Health Perception	-0.79(-7.24, 5.66)	0.81	-4.14(-10.05, 1.76)	0.169

Demographics variables are age, gender, ethnicity, disease duration and region. Combination DMARDs is the reference group where appropriate

Table 10: **Primary Outcome And Other Key Secondary Outcomes In Intention To Treat Population In Combination DMARD Group (N=104) Individual Mean And 95% Confidence Intervals Scores Shown By Patients Staying On DMARDs Or Switching To TNFis**

Measures	**Stayed on Combination DMARD (n=58)**				**Changed to TNF Inhibitors (n=46)**			
	Initial	*6 month*	*12 month*	*Change 0-12*	*Initial*	*6 month*	*12 month*	*Change 0-12*
HAQ	1.82 [1.65, 1.98]	1.42 [1.23, 1.60]	1.38 [1.17,1.60]	0.43[a] [0.29, 0.58]	1.77 [1.62, 1.92]	1.64 [1.46, 1.82]	1.31 [1.10, 1.51]	0.46 [0.30, 0.62]
EQ5D	0.35 [0.27, 0.43]	0.57 [0.50, 0.64]	0.61 [0.53,0.69]	-0.26[b] [-0.35, -0.17]	0.44 [0.35, 0.52]	0.49 [0.40, 0.57]	0.57 [0.48, 0.65]	-0.13 [-0.24, -0.02]
Larsen Score	44.7 [33.6, 55.8]	45.3 [34.1, 56.5]	45.9 [34.7, 57.0]	-1.13[c] [-2.63, 0.38]	45.5 [33.4, 57.6]	46.5 [34.3, 58.7]	46.9 [34.6 ,59.3]	-1.43 [-2.92, 0.06]

a. P= 0.81 comparing change at 12 months between groups by linear regression

b. P= 0.069 comparing change at 12 months between groups by linear regression

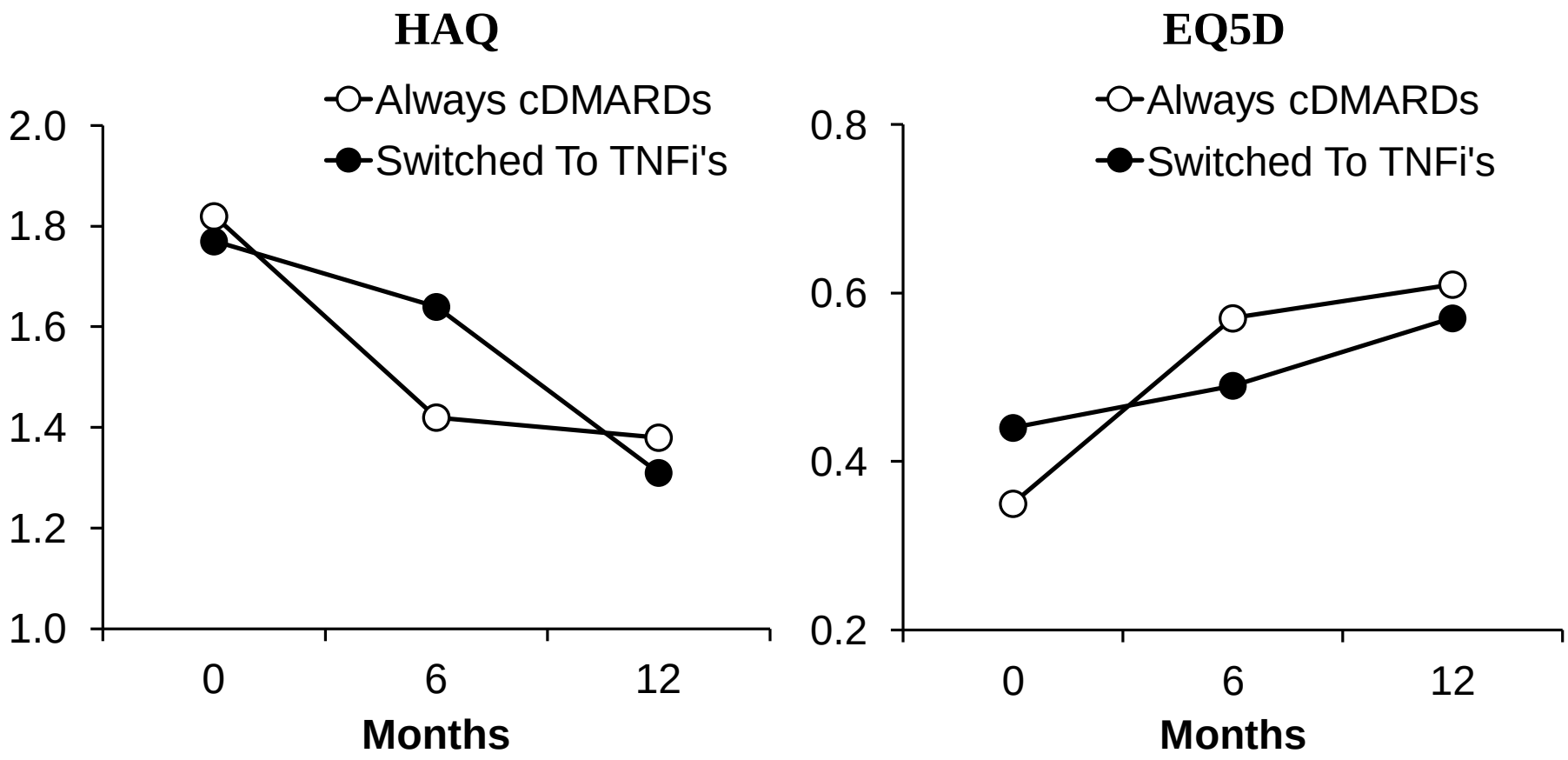
c. P=0.77 comparing change at 12 months between groups by linear regression

Table 11 Adjusted And Unadjusted Treatment Effect Using Generalised Estimating Equations For Primary Outcome Measure (HAQ) in Combination DMARD Arm In Patients Remaining On DMARDs And Changing To Tumour Necrosis Factor Inhibitors In Intention To Treat Population

Change In HAQ	**Model 1 (Unadjusted) Treatment +Region +Time**		**Model 2 (Adjusted) Treatment + demographics + baseline score + Time**	
	Coefficient (95% CI)	*p-value*	*Coefficient (95% CI)*	*p-value*
12 months	0.14 (-0.03, 0.31)	0.103	0.12 (-0.05, 0.29)	0.185

Demographics variables are age, gender, ethnicity, disease duration and region. No switch is the reference group

Figure 3: Mean HAQ And EQ5D Scores In Patients In cDMARD Arm In Intention To Treat Population. Mean Scores Are Shown For Patients Remaining On cDMARDs And Switching To TNFI's



11.4.1.1.4 Changes In Larsen Score

A. Intention To Treat Population

The initial Larsen scores differed between groups (Table 6): in the cDMARD group the initial mean score was 45.1 (95% CI 37.0, 53.2); in the TNFi group it was 37.9 (95% CI 30.2, 45.6). The Larsen scores were the only clinical variable to show baseline differences and no clinical significance was attached to this difference.

Progression over 12 months was similar (Figure 4) between groups. With cDMARDs Larsen Scores increased by 1.26 and with TNFis they increased by 1.37. Progression over 6 months was also similar. These differences were not statistically significant between the treatment groups (Tables 8 and 10).

An exploratory analysis examined individual changes over 12 months using all observed data for both groups (Figure 5); this showed no evidence of a different pattern of progression between the groups.

Another exploratory analysis evaluated the development of one (increase in Larsen Score of 2-5) or many new erosions (increase in Larsen Score of more than 5) using all observed data for both groups; this is summarized in Figure 6. There were no differences between groups. By the end of trial, 23 of 91 (25%) of patients randomized to receive cDMARDs developed one new erosion and 12 of 91 (14%) developed two or more. 19 of 93 (20%) of patients randomized to receive TNFis developed one new erosion and 13 of 93 (14%) developed two or more.

Over 12 months both sets of patients had small increases in Larsen scores (Table 10 and Figure 4); in patients remaining on cDMARDs Larsen scores increased by a mean of -1.13 (95% CI -2.63, 0.38,) and in patients switching to TNFis Larsen scored increased by a mean of -1.43 (95% CI -2.92, 0.06). Comparing these changes in Larsen score over 12 months by linear regression showed no evidence the difference was significant (Table 10). We also examined individual changes over 12 months using all observed data for both sets of patients (Figure 7); this showed no evidence of a different pattern of progression between the sub-sets

B. Complete Case Analysis

Changes in Larsen scores were similar in patients randomised to cDMARDs and TNFis. There was no evidence of a significant difference between groups (Appendix 2 Tables 1 and 4).

Figure 4: Mean Larsen Scores In Intention To Treat Population. Mean Scores Are Shown For Both Groups And For The cDMARD Group For Patients Remaining On cDMARDs And Switching To TNFI's

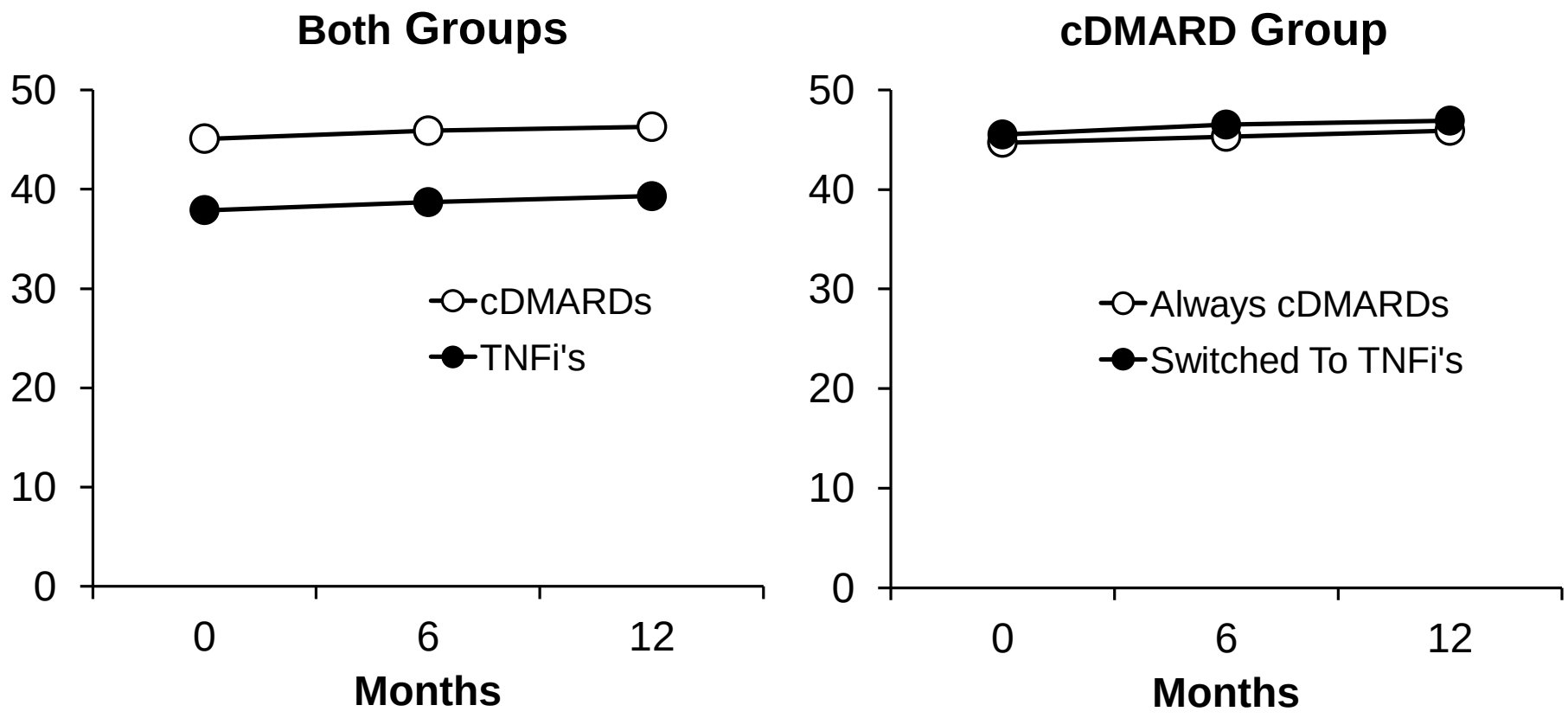


Figure 5: Individual Changes Over 12 Months In Larsen Scores Using All Collected Data For Both Groups

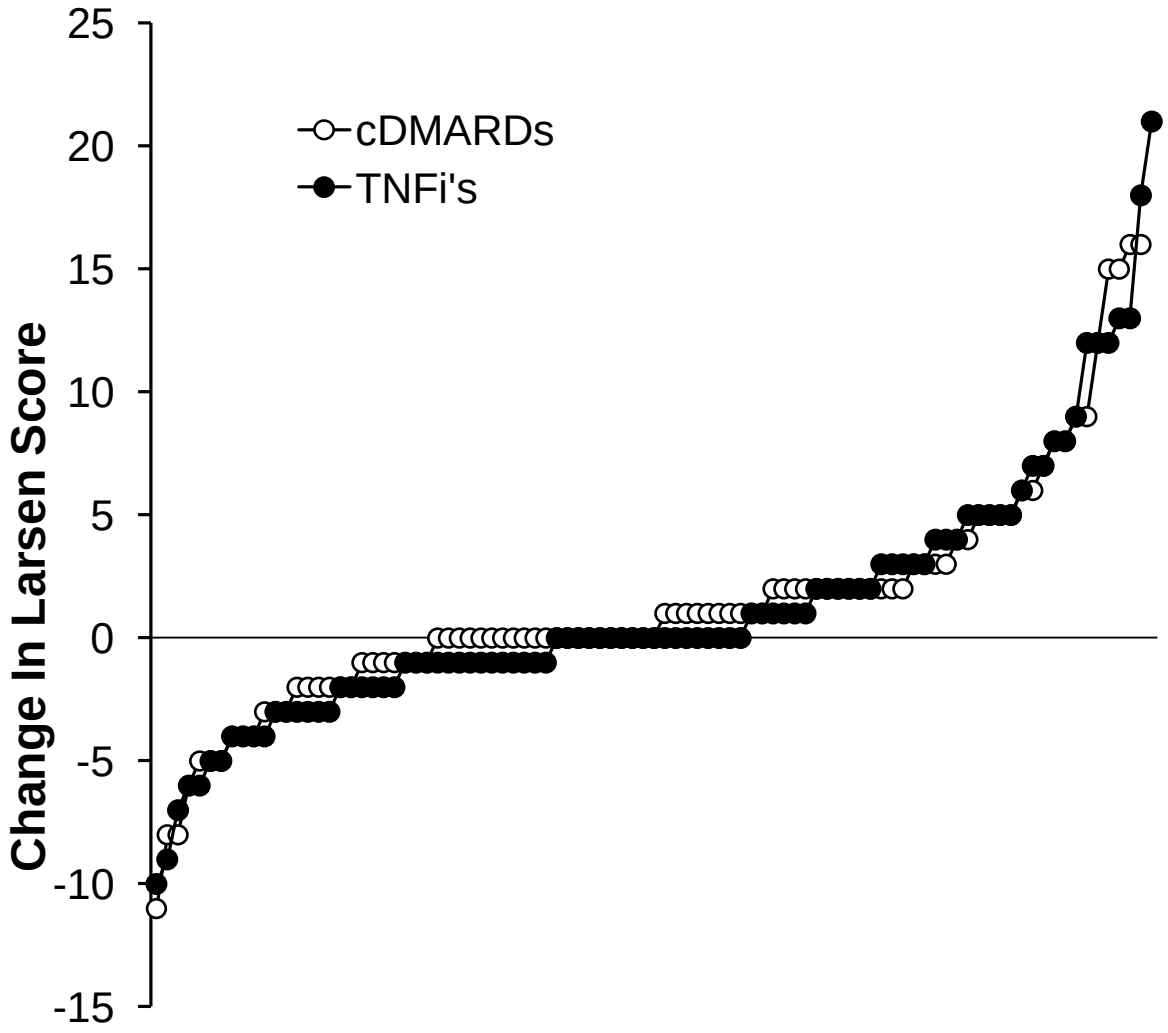


Figure 6: Development Of New Erosions Over 12 Months Using All Observed Data For Both Groups

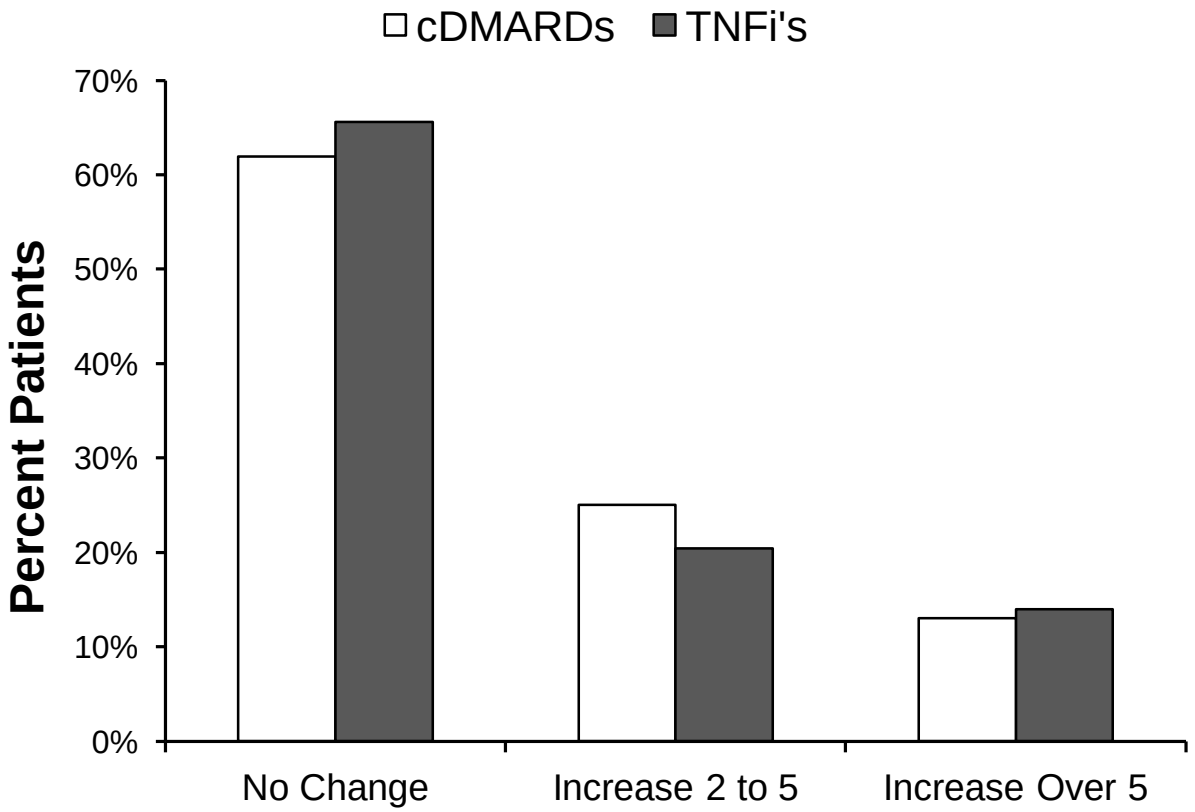
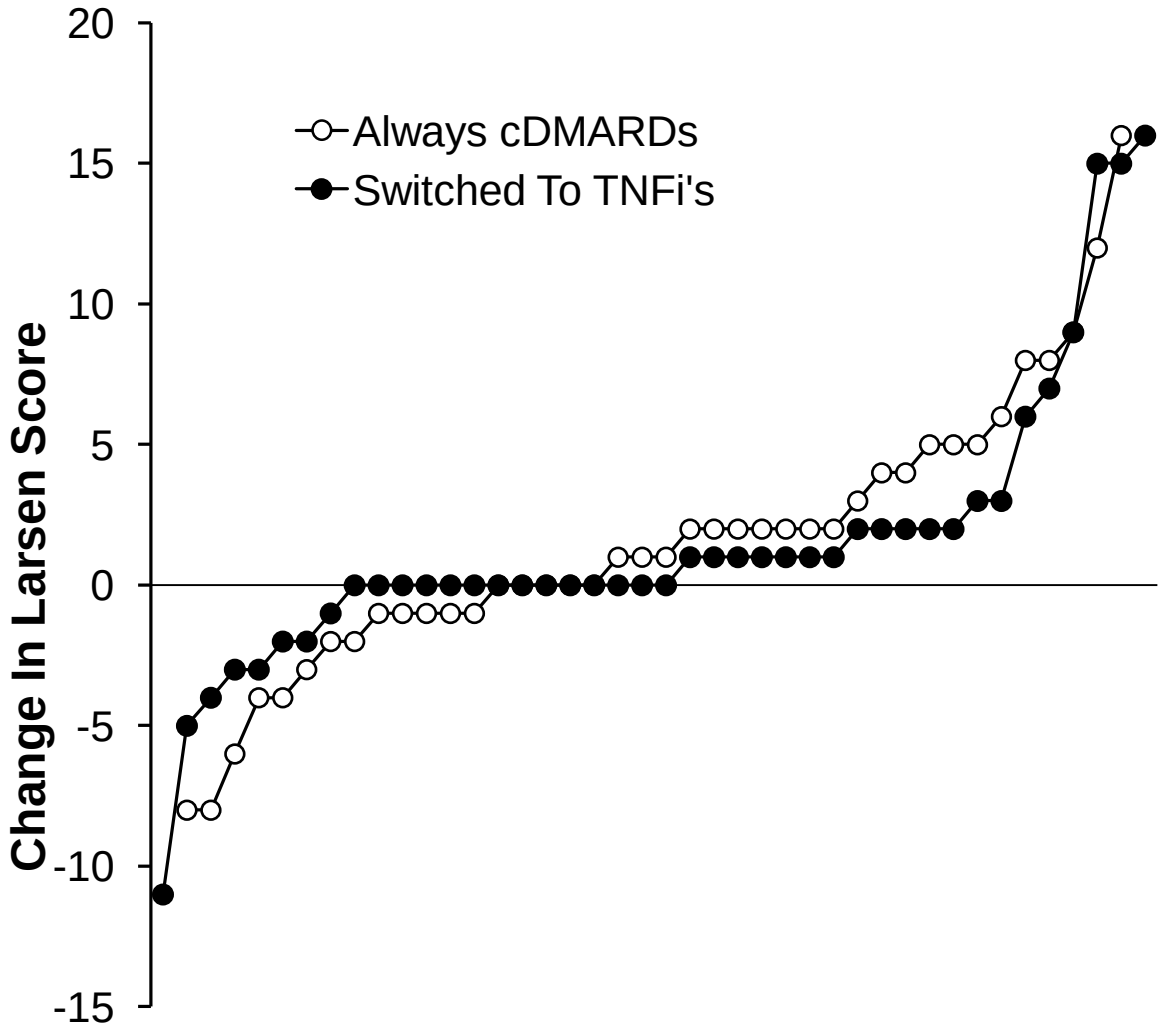


Figure 7: Individual Changes Over 12 Months In Larsen Scores In cDMARD Group Using All Observed Data Divided Into Patients Remaining On cDMARDs And Switching To TNFI's



11.4.1.2 Disease Activity Scores (Assessed Every Month)

Outcomes which were collected monthly comprised DAS28 and its components – tender joint counts, swollen joint counts, erythrocyte sedimentation rate and visual analogue scale patient global assessments. We assessed changes in DAS28, changes in its components in the intention to treat population. We also assessed the occurrence of a clinical response (decrease in DAS28 of ≥1.2) and low DAS28 scores indicative of remissions (DAS28 ≤2.6) using all observed data; imputation was not undertaken for this summary data because evaluating clinical responses and DAS28 remissions were exploratory analyses rather than predefined analyses as explained in the statistical analysis plan (methods section).

11.4.1.2.1 Changes in DAS28

A. Intention To Treat Population

Initial DAS28 scores were similar in both groups (Table 12): in the cDMARD group initial mean DAS28 was 6.21 (95% CI 6.04, 6.39) and in the TNFi group 6.30 (95% CI 6.14, 6.46). By 6 months DAS28 had fallen with cDMARDs to 4.78 (95% CI 4.45, 5.12) and with TNFis to 4.23 (95% CI 3.89, 4.58). By 12 months DAS28 had further fallen with cDMARDs to 4.04 (95% CI 3.74, 4.34) and with TNFis to 3.89 (95% CI 3.53, 4.24). The initial change in DAS28 scores was greater in patients randomised to TNFis and there was a significant difference between groups within the first month of treatment. After one month mean DAS28 with cDMARDs fell to 5.32 (95% CI 5.05, 5.59) and with TNFis to 4.67 (95% CI 4.38, 4.95; p=0.001).

Longitudinal analysis (Table 13) showed there was a significant difference between treatment groups over the whole 12 month period. Patients randomised to TNFis achieved greater overall reductions in DAS28 than those randomised to cDMARDs in both the unadjusted (-0.48; 95% CI -0.79, -0.17; p=0.002) and the adjusted models (-0.40; 95% CI -0.69, -0.10; p=0.009). Comparing initial and final treatment periods showed a difference in the pattern of change. In the first six months there was a greater reduction in DAS28 in patients randomised to TNFis than in patients randomised to cDMARDs; the coefficient was -0.63 (95% CI -0.93,-0.34; p<0.001). In the second period there was no difference between groups; the coefficient was -0.19 (95% CI -0.55, 0.18; p=0.317).

B. Complete Case Analysis

Mean DAS28 scores fell in both groups with treatment (Appendix 2 Table 6 and Figure 2). Longitudinal analysis using generalised estimating equations with AR (1) correlation showed the decreases were significantly greater with TNFis (Appendix 2 Table 7) in both unadjusted (P<0.001) and adjusted models (P<0.001).

11.4.1.2.2 Changes in DAS28 Components

A. Intention To Treat Population

Baseline tender joint counts, swollen joint counts, ESR and patient global assessments were similar in both groups and they all improved when patients received either cDMARDs or TNFis. The patterns of change are shown in Table 12 and Figures 9 and 10.

Longitudinal analysis (Table 13) showed that in the overall adjusted model changes in the ESR were significantly different between patients randomised to cDMARDs and those randomised to TNFis; the decrease was significantly larger with TNFis (coefficient -4.62(95% CI -7.77, -1.47; p=0.004). The other components showed no significant differences between treatment groups over the whole 6 months.

In the first six months of treatment the adjusted mean treatment effects for all the components were significantly greater in patients randomised to TNFis than in those randomised to cDMARDs. In the second six months there were no statistically significant differences between groups.

The speed of onset of changes was particularly marked in the ESR in patients randomised to TNFis. With cDMARDs the ESR fell from an initial mean of 33.1 (95% CI 28.1, 38.2) to 32.4 (95% CI 27.4, 37.5) by one month. With TNFis the ESR fell from an initial mean of 30.1 (95% CI 25.7, 34.6) to 19.6 (95% CI 15.8, 23.3) by one month.

B. Complete Case Analysis

Tender joint counts, swollen joint counts, ESR and patient global assessments all improved with patients received either cDMARDs or TNFis (Appendix 2 Table 6, Figure 3 and Figure 4). Longitudinal analysis (Appendix 2 Table 7) showed the decreases were significantly greater with TNFis for tender joint counts, swollen joint counts and ESR in both unadjusted and adjusted models.

Patients were selected to switch from cDMARDs to TNFis after 6 months if they had failed to achieve reductions in DAS28 scores of less than 1.2. As a consequence mean DAS28 scores in the switchers would be expected to be less than in those who remained on cDMARDs. This difference is shown in Table 14, together with changes in the individual components of the DAS28 scores. It is also illustrated in Figure 11. The difference is confirmed to be significant in the longitudinal analysis shown in Table 15. The adjusted models showed a significant reduction in DAS28 scores in the switchers. The same effect was seen in the components of DAS28 and was most marked with tender joint counts and patients global VAS scores.

Table 12: Individual Mean (95% Confidence Intervals) For Disease Activity Score And Its Components In Intention To Treat Population

Month Of Assessment	**Combination DMARDs (n=104)**					**TNF Inhibitors (n=101)**				
	DAS28	*Tender Joint Counts*	*Swollen Joint Counts*	*ESR*	*VAS*	*DAS28*	*Tender Joint Counts*	*Swollen Joint Counts*	*ESR*	*VAS*
	Mean [95 % CI]	*Mean [95 % CI]*	*Mean [95 % CI]*	*Mean [95 % CI]*	*Mean [95 % CI]*	*Mean [95 % CI]*	*Mean [95 % CI]*	*Mean [95 % CI]*	*Mean [95 % CI]*	*Mean [95 % CI]*
0	6.21 [6.04,6.39]	16.38 [15.02,17.75]	10.51 [9.34,11.68]	33.14 [28.10,38.19]	68.13 [64.32,71.95]	6.30 [6.14,6.46]	17.48 [16.15,18.80]	10.79 [9.47,12.11]	30.13 [25.65,34.61]	68.18 [64.00,72.36]
1	5.32 [5.05,5.59]	11.81 [10.07,13.56]	6.76 [5.55,7.97]	32.44 [27.43,37.46]	54.87 [49.90,59.84]	4.67 [4.38,4.95]	10.69 [8.93,12.46]	5.76 [4.53,6.99]	19.56 [15.78,23.34]	46.15 [41.09,51.20]
2	5.02 [4.76,5.27]	9.85 [8.36,11.34]	5.72 [4.72,6.72]	30.23 [25.51,34.95]	51.96 [47.22,56.70]	4.30 [3.98,4.61]	7.84 [6.47,9.21]	5.02 [3.74,6.31]	21.54 [17.27,25.81]	43.18 [38.14,48.22]
3	4.92 [4.63,5.21]	9.97 [8.36,11.59]	5.37 [4.26,6.47]	30.10 [24.81,35.39]	50.94 [45.74,56.15]	4.28 [3.95,4.60]	7.71 [6.12,9.31]	4.43 [3.27,5.59]	23.44 [19.08,27.80]	43.16 [38.10,48.23]
4	4.73 [4.45,5.02]	8.40 [7.03,9.78]	4.91 [3.85,5.97]	31.20 [26.05,36.36]	45.38 [39.69,51.07]	4.31 [3.97,4.64]	8.16 [6.54,9.78]	4.07 [2.95,5.20]	22.23 [18.31,26.15]	45.40 [39.48,51.31]
5	4.66 [4.36,4.96]	8.51 [6.98,10.04]	5.44 [4.33,6.55]	29.87 [24.95,34.79]	43.62 [37.87,49.37]	4.13 [3.81,4.44]	7.75 [6.06,9.45]	4.38 [3.15,5.62]	20.51 [16.96,24.06]	40.60 [35.02,46.18]
6	4.78 [4.45,5.12]	10.16 [8.39,11.93]	6.11 [4.74,7.49]	29.25 [24.16,34.33]	48.25 [42.42,54.09]	4.23 [3.89,4.58]	8.57 [6.87,10.27]	4.66 [3.41,5.90]	21.80 [17.64,25.96]	40.51 [34.98,46.03]
7	4.57	8.34	5.76	28.21	42.51	4.17	8.01	4.64	21.01	40.73

Month Of Assessment	**Combination DMARDs (n=104)**					**TNF Inhibitors (n=101)**				
	DAS28	*Tender Joint Counts*	*Swollen Joint Counts*	*ESR*	*VAS*	*DAS28*	*Tender Joint Counts*	*Swollen Joint Counts*	*ESR*	*VAS*
	Mean	*Mean*	*Mean*	*Mean*	*Mean*	*Mean*	*Mean*	*Mean*	*Mean*	*Mean*
	[95 % CI]	*[95 % CI]*	*[95 % CI]*	*[95 % CI]*	*[95 % CI]*	*[95 % CI]*	*[95 % CI]*	*[95 % CI]*	*[95 % CI]*	*[95 % CI]*
8	[4.27,4.87]	[6.68,10.01]	[4.53,7.00]	[23.03,33.39]	[36.95,48.07]	[3.81,4.53]	[6.35,9.67]	[3.34,5.93]	[17.18,24.85]	[34.72,46.73]
	4.25	7.42	4.54	24.14	41.30	4.05	6.62	4.23	21.77	42.56
	[3.92,4.59]	[5.98,8.85]	[3.43,5.64]	[19.29,28.99]	[35.45,47.14]	[3.69,4.41]	[5.14,8.09]	[3.04,5.42]	[17.57,25.97]	[36.91,48.22]
9	4.21	6.93	3.99	25.47	41.56	4.08	6.68	4.30	22.92	40.86
	[3.87,4.56]	[5.40,8.47]	[2.98,5.00]	[20.57,30.37]	[35.78,47.35]	[3.73,4.42]	[5.14,8.22]	[3.07,5.52]	[18.62,27.21]	[35.36,46.36]
10	4.05	6.17	3.69	25.42	38.33	3.90	6.51	3.42	21.48	39.33
	[3.73,4.37]	[4.74,7.60]	[2.78,4.61]	[20.44,30.40]	[33.02,43.65]	[3.56,4.24]	[4.90,8.12]	[2.33,4.51]	[17.34,25.62]	[33.64,45.03]
11	4.03	6.67	3.27	23.28	40.64	3.84	6.16	3.50	22.01	37.69
	[3.74,4.31]	[5.09,8.25]	[2.31,4.24]	[18.69,27.87]	[34.69,46.59]	[3.48,4.20]	[4.57,7.76]	[2.25,4.75]	[17.73,26.28]	[31.82,43.56]
12	4.04	6.32	3.39	25.03	39.21	3.89	6.81	3.20	20.32	43.03
	[3.74,4.34]	[4.88,7.77]	[2.63,4.14]	[20.41,29.65]	[33.23,45.19]	[3.53,4.24]	[5.22,8.40]	[2.25,4.14]	[16.04,24.59]	[36.79,49.27]

Figure 8: Mean Changes In DAS28 With Treatment In Intention To Treat Population

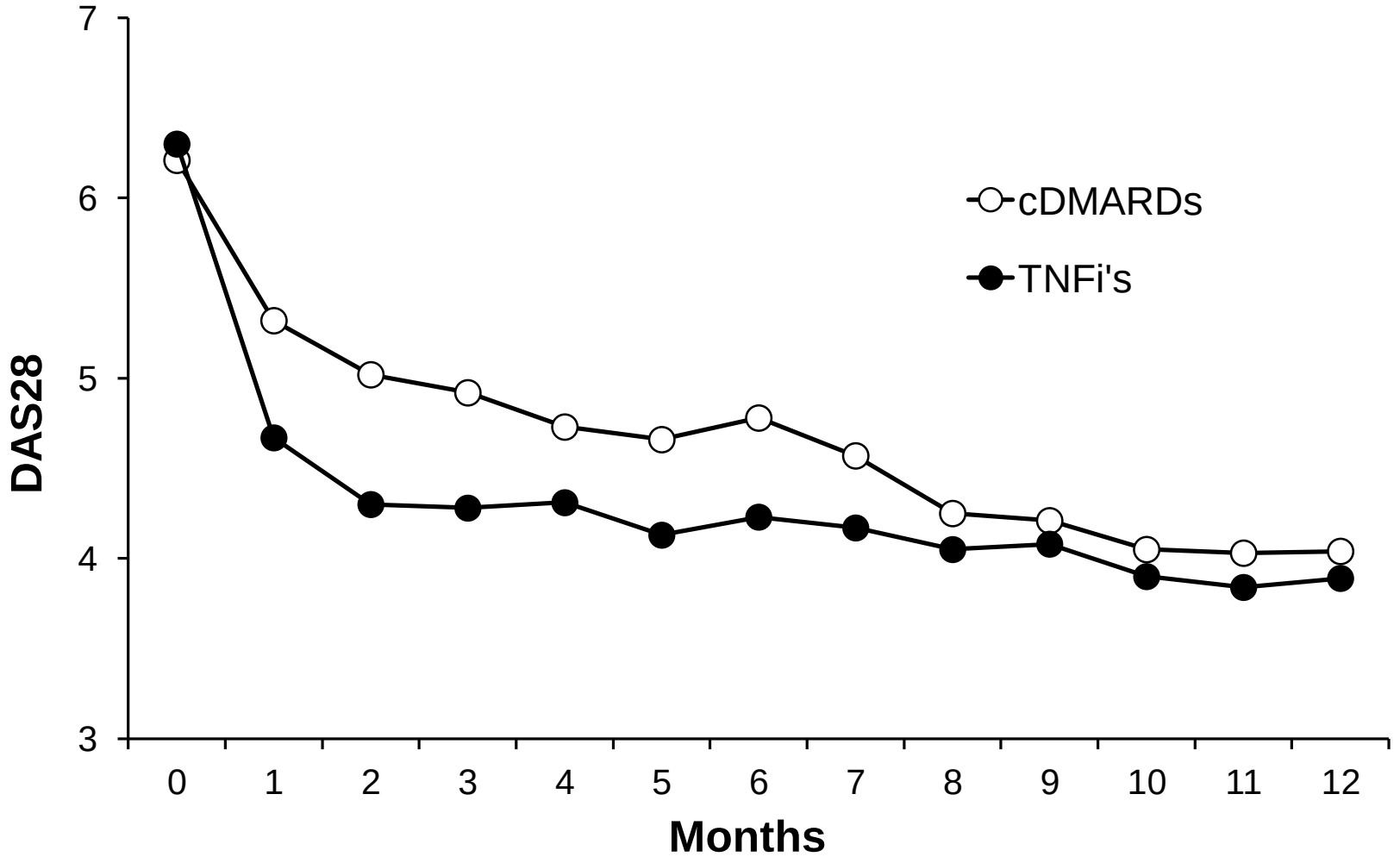


Figure 9: Mean Changes In Tender And Swollen Joint counts With Treatment In Intention To Treat Population

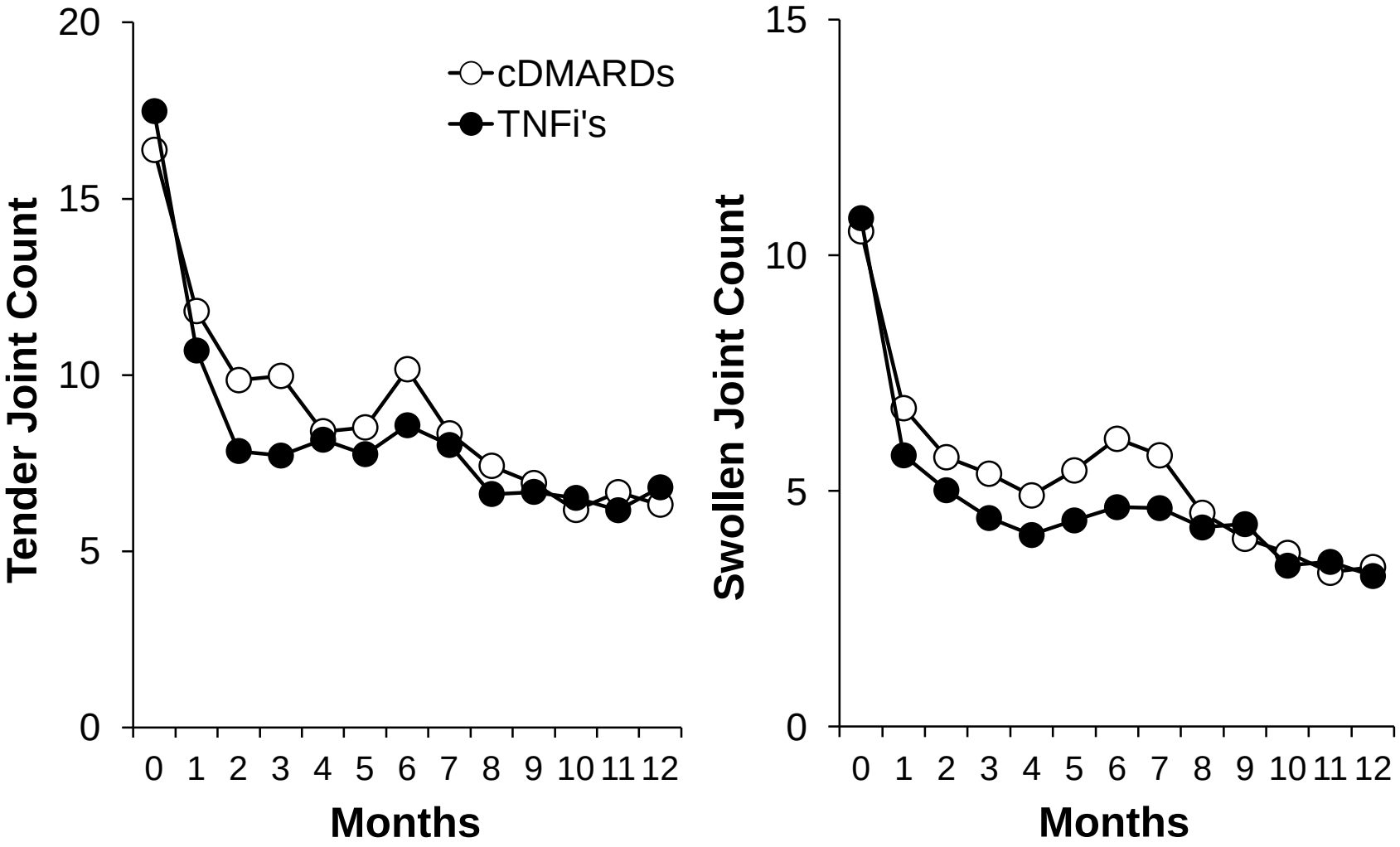


Figure 10: Mean Changes In ESR And Patient Global VAS With Treatment In Both Groups In Intention To Treat Population

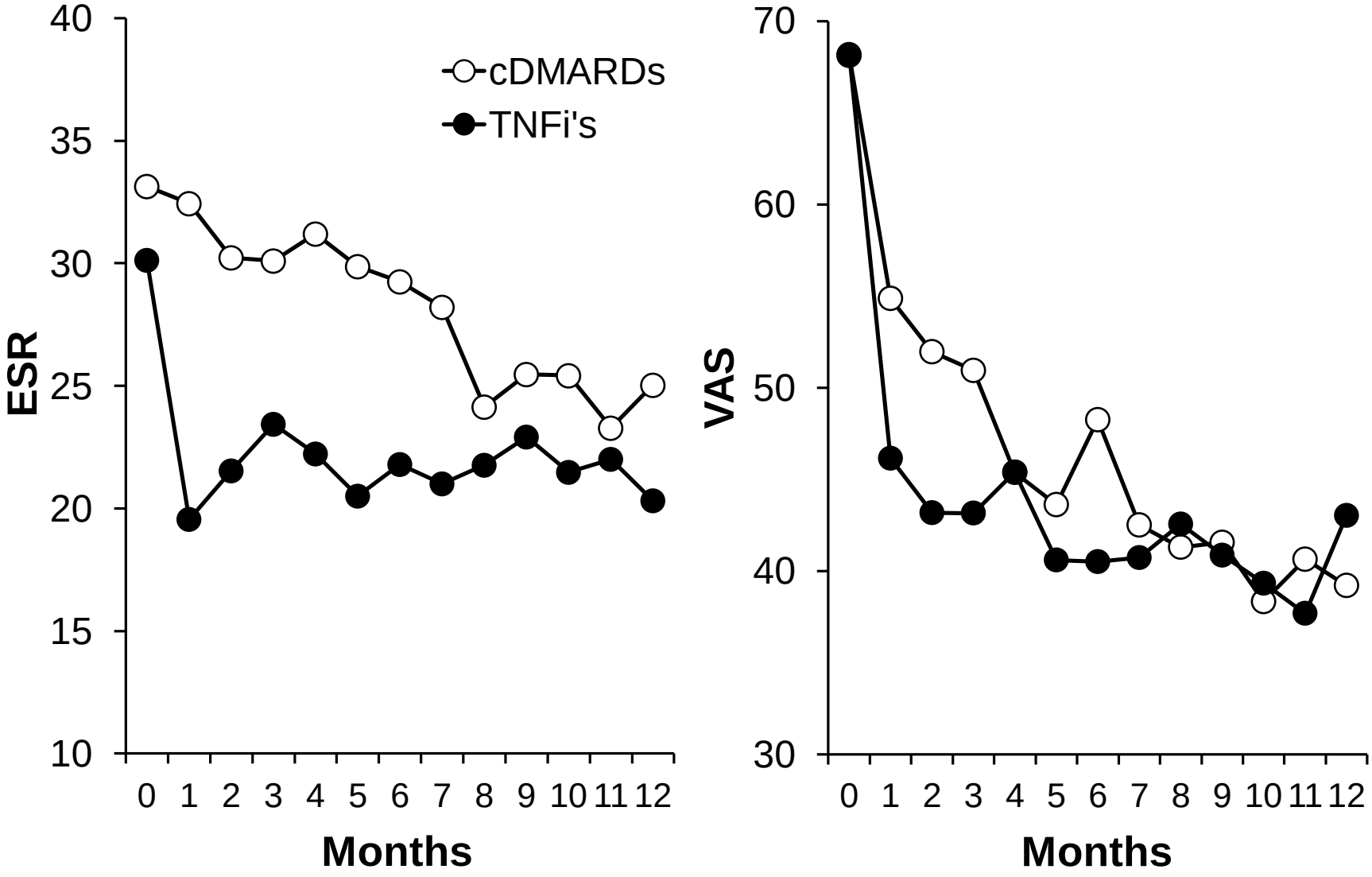


Table 13: Longitudinal Analysis Comparing Effect Of Randomised Treatment Arm On Disease Activity Score (DAS28) And Its Components In Intention To Treat Population Using Generalised Estimating Equations

Time Period	**Variable**	**Model 1 (Unadjusted) Treatment + Region + Time**		**Model 2 (Adjusted) Treatment + demographics + baseline score**	
		Coefficient (95% CI)	*p-value*	*Coefficient (95% CI)*	*p-value*
Months 1-6	DAS28	-0.68 (-0.99, -0.37)	<0.001	-0.63 (-0.93, -0.34)	<0.001
	Tender Joint Count	-2.42 (-4.22, -0.63)	0.008	-1.79 (-3.31, -0.26)	0.022
	Swollen Joint Count	-1.35 (-2.76, 0.07)	0.062	-1.16 (-2.20, -0.12)	0.029
	ESR	-6.46(-10.23, -2.68)	0.001	-7.18(-10.60, -3.76)	<0.001
	VAS	-6.97(-13.10, -0.84)	0.026	-6.41(-11.66, -1.15)	0.017
Months 7-12	DAS28	-0.31 (-0.69, 0.07)	0.111	-0.19 (-0.55, 0.18)	0.317
	Tender Joint Count	-1.10 (-3.22, 1.01)	0.307	-0.13 (-1.79, 1.53)	0.879
	Swollen Joint Count	-0.69 (-2.27, 0.88)	0.388	-0.31 (-1.36, 0.75)	0.570
	ESR	-1.63(-5.88, 2.62)	0.452	-2.15(-5.73, 1.44)	0.[154]
	VAS	0.60(-6.47, 7.67)	0.867	2.04(-4.08, 8.17)	0.513
Months 1-12	DAS28	-0.48 (-0.79, -0.17)	0.002	-0.40 (-0.69, -0.10)	0.009
	Tender Joint Count	-1.69 (-3.50, 0.11)	0.066	-0.93 (-2.36, 0.51)	0.205
	Swollen Joint Count	-0.86 (-2.27, 0.55)	0.233	-0.63 (-1.57, 0.31)	0.186
	ESR	-4.04 (-7.67, -0.40)	0.029	-4.62 (-7.77, -1.47)	0.004
	VAS	-2.83 (-8.85, 3.20)	0.358	-1.96 (-7.04, 3.11)	0.448

Demographics variables are age, gender, ethnicity, disease duration and region; Combination DMARDs is the reference group

Table 14: Individual Mean (95% Confidence Intervals) For Disease Activity Score And Its Components In Intention To Treat Population In Combination DMARD Group (N=104) Individual Mean And 95% Confidence Intervals Scores Shown By Patients Staying On DMARDs Or Switching To TNFis

Month Of Assessment	**Staying on DMARDs (n=58)**					**Switching To TNF Inhibitors (n=46)**				
	DAS28	*Tender joint counts*	*Swollen joint counts*	*ESR*	*VAS*	*DAS28*	*Tender joint counts*	*Swollen joint counts*	*ESR*	*VAS*
	Mean [95 % CI]	*Mean [95 % CI]*	*Mean [95 % CI]*	*Mean [95 % CI]*	*Mean [95 % CI]*	*Mean [95 % CI]*	*Mean [95 % CI]*	*Mean [95 % CI]*	*Mean [95 % CI]*	*Mean [95 % CI]*
0	6.10 [5.84,6.35]	15.05 [13.11,16.99]	9.95 [8.45,11.44]	34.07 [27.29,40.85]	69.50 [64.19,74.81]	6.36 [6.12,6.60]	18.07 [16.24,19.89]	11.22 [9.34,13.10]	31.98 [24.26,39.70]	66.41 [60.88,71.95]
1	5.06 [4.69,5.42]	10.14 [7.78,12.49]	5.72 [4.39,7.06]	32.76 [26.01,39.50]	52.23 [45.54,58.92]	5.66 [5.26,6.05]	13.92 [11.39,16.46]	8.07 [5.93,10.21]	32.05 [24.35,39.74]	58.21 [50.74,65.68]
2	4.74 [4.40,5.07]	8.17 [6.33,10.00]	4.70 [3.49,5.92]	30.11 [24.05,36.18]	49.69 [43.34,56.05]	5.37 [4.99,5.75]	11.97 [9.64,14.30]	7.01 [5.38,8.64]	30.38 [22.77,37.98]	54.81 [47.50,62.13]
3	4.64 [4.27,5.01]	8.54 [6.58,10.50]	4.59 [3.08,6.09]	28.94 [21.86,36.03]	48.80 [41.44,56.16]	5.27 [4.81,5.72]	11.77 [9.12,14.42]	6.35 [4.69,8.00]	31.55 [23.45,39.66]	53.65 [46.32,60.98]
4	4.51 [4.15,4.87]	7.04 [5.44,8.64]	3.80 [2.59,5.00]	31.11 [23.79,38.43]	44.47 [36.92,52.02]	5.01 [4.54,5.49]	10.13 [7.78,12.47]	6.32 [4.52,8.12]	31.32 [24.17,38.47]	46.52 [37.63,55.41]
5	4.27 [3.90,4.65]	6.43 [4.64,8.23]	3.64 [2.46,4.81]	29.31 [22.87,35.76]	39.13 [31.94,46.32]	5.15 [4.68,5.62]	11.13 [8.73,13.53]	7.72 [5.85,9.59]	30.57 [22.88,38.27]	49.28 [40.01,58.55]
6	4.01 [3.61,4.40]	6.27 [4.35,8.19]	3.20 [1.78,4.62]	27.66 [20.92,34.40]	37.26 [29.75,44.78	5.76 [5.32,6.19]	15.07 [12.47,17.66]	9.78 [7.65,11.91]	31.24 [23.35,39.14]	62.11 [54.51,69.71]

Month Of Assessment	**Staying on DMARDs (n=58)**					**Switching To TNF Inhibitors (n=46)**				
	DAS28	*Tender joint counts*	*Swollen joint counts*	*ESR*	*VAS*	*DAS28*	*Tender joint counts*	*Swollen joint counts*	*ESR*	*VAS*
	Mean [95 % CI]	*Mean [95 % CI]*	*Mean [95 % CI]*	*Mean [95 % CI]*	*Mean [95 % CI]*	*Mean [95 % CI]*	*Mean [95 % CI]*	*Mean [95 % CI]*	*Mean [95 % CI]*	*Mean [95 % CI]*
7	4.09 [3.71,4.46]	5.85 [3.79,7.90]	3.91 [2.40,5.41]	28.87 [21.57,36.18]	38.04 [30.16,45.92]	5.18 [4.74,5.61]	11.49 [8.97,14.01]	8.11 [6.25,9.97]	27.37 [20.00,34.74]	48.15 [40.36,55.93]
8	4.13 [3.68,4.58]	6.26 [4.51,8.00]	3.55 [2.23,4.86]	24.88 [18.17,31.58]	42.35 [34.19,50.50]	4.41 [3.91,4.92]	8.87 [6.54,11.21]	5.79 [3.97,7.60]	23.20 [16.01,30.40]	39.97 [31.60,48.34]
9	4.15 [3.69,4.62]	5.75 [3.87,7.63]	3.46 [2.12,4.81]	26.58 [20.08,33.07]	43.31 [34.89,51.73]	4.29 [3.78,4.80]	8.43 [6.02,10.84]	4.64 [3.03,6.26]	24.07 [16.40,31.74]	39.36 [31.28,47.44]
10	3.91 [3.48,4.34]	5.23 [3.51,6.96]	3.35 [2.11,4.59]	25.67 [18.55,32.80]	37.16 [29.52,44.81]	4.23 [3.75,4.72]	7.35 [5.03,9.67]	4.12 [2.77,5.48]	25.10 [18.29,31.92]	39.81 [32.33,47.29]
11	3.87 [3.48,4.25]	5.44 [3.54,7.33]	2.63 [1.40,3.85]	22.65 [16.69,28.61]	40.56 [31.84,49.27]	4.23 [3.77,4.69]	8.22 [5.66,10.78]	4.09 [2.53,5.65]	24.08 [16.79,31.38]	40.74 [32.36,49.13]
12	3.91 [3.52,4.31]	5.37 [3.66,7.08]	2.87 [1.83,3.91]	26.39 [20.45,32.33]	38.33 [29.89,46.78	4.19 [3.73,4.66]	7.52 [5.08,9.97]	4.04 [2.93,5.15]	23.33 [15.89,30.76]	40.32 [31.89,48.75]

Figure 11: Mean DAS28 In Patients In cDMARD Arm In Intention To Treat Population. Mean Scores Are Shown For Patients Remaining On cDMARDs And Switching To TNFI's

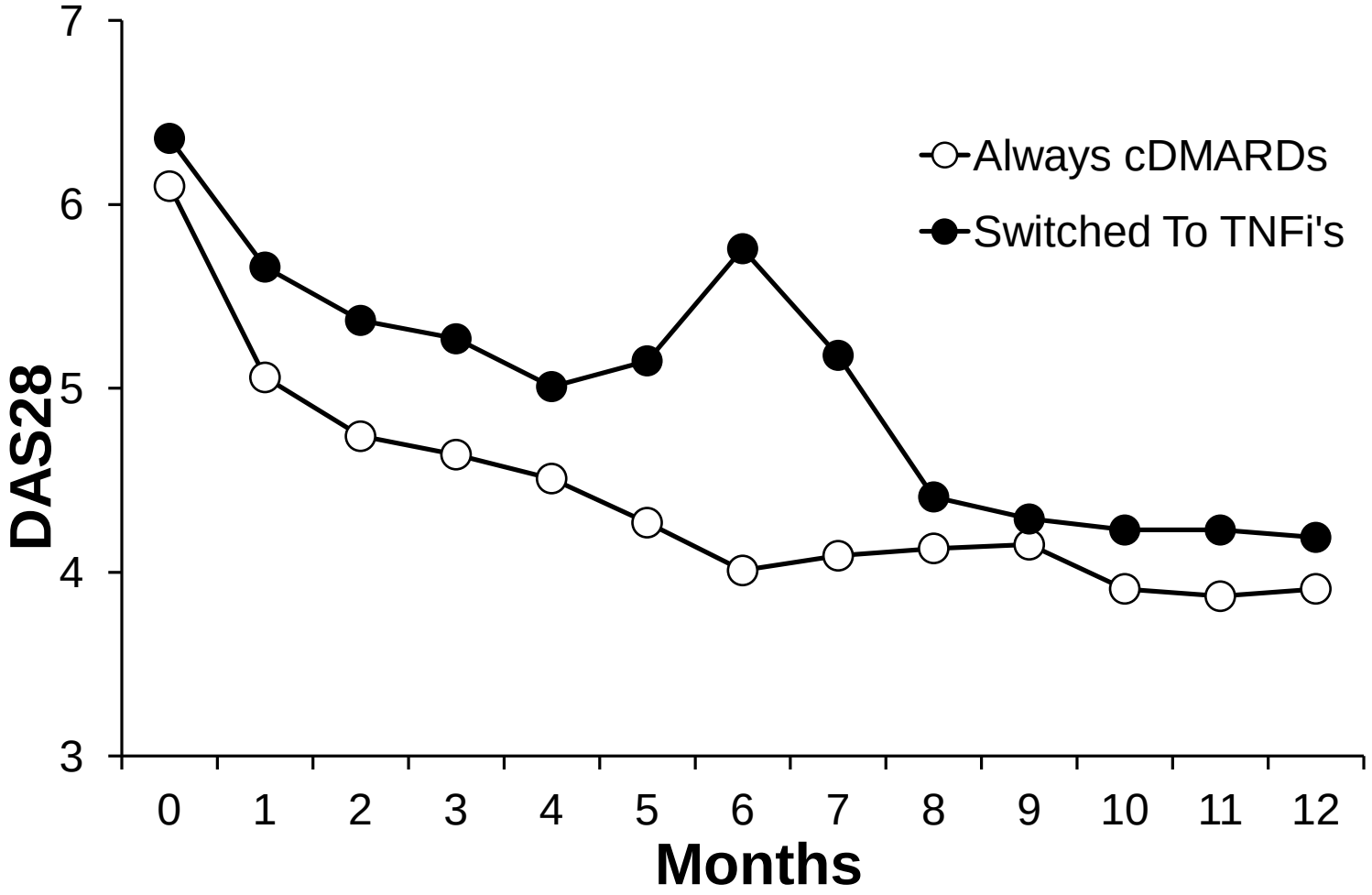


Table 15: Longitudinal Analysis Comparing Effect Of Randomised Treatment Arm On Disease Activity Score (DAS28) And Its Components In Patients Who Switched Arm After 6 Months Using Generalised Estimating Equations In Intention To Treat Population

Variable	**Model 1 (Unadjusted)** **Treatment +Region + Time**		**Model 2 (Adjusted)** **Treatment + demographics + baseline score**	
	Coefficient (95% CI)	*p-value*	*Coefficient (95% CI)*	*p-value*
DAS28	0.35 (-0.03, 0.74)	0.071	0.51 (0.16, 0.86)	0.005
Tender Joint Count	0.69 (-1.47, 2.85)	0.532	2.42 (0.75, 4.10)	0.004
Swollen Joint Count	0.97 (-1.04, 2.97)	0.344	1.94 (0.65, 3.22)	0.003
ESR	2.54 (-2.65, 7.73)	0.338	2.44 (-1.97, 6.84)	0.278
VAS	10.26 (2.70, 17.83)	0.008	8.29 (2.14, 14.44)	0.008

Demographics variables are age, gender, ethnicity, disease duration and region. No switch is the reference group

11.4.1.3 Achieving Clinical Responses

11.4.1.3.1 Time To Achieve Responses

An exploratory analysis examined the time taken to achieve clinically meaningful responses - decreases in DAS28 scores of ≥1.2. The times to achieve responses were compared between groups using Kaplan Meier plots. These results are shown in Figure 12. 98 of 104 (94%) of patients randomised to receive cDMARDs and 94 of 101 (93%) of patients randomised to receive TNFis achieved such responses. The responses occurred sooner in the patients randomised to TNFis and this difference was significant in a log rank test (p=0.035). Patients randomised to receive cDMARDs who had DAS28 responses achieved them within a mean of 3 months. Patients randomised to receive TNFis who had DAS28 responses achieved them within a mean of 2 months.

11.4.1.3.2 Persistence Of Response

There was a complex pattern of achieving responses. In some patients responses were persistent and in others they were unsustained. Examples of these variations are shown for 4 patients randomised to the TNFi group in Figure 13. As a consequence of these variations we evaluated the frequencies of responses each month; these are shown in Figure 14. There was a different pattern of responses between groups. Patients randomised to cDMARDs showed a gradual increase in the rate of responses from 45% or less at 3 months or earlier to over 70% by 10 months. By contrast patients randomised to TNFis achieved a response rate over 70% by 2 months and the response rate remained above 70% thereafter; its highest was 84% (achieved at month 11).

11.4.1.3.3 Impact Of Switching cDMARDs to TNFis

There was a difference in the patients randomised to cDMARDs who remained on cDMARDs and those who switched to TNFis. This is shown in Figure 15. Patients remaining on cDMARDs had response rates over 50% from 2 months onwards and after 6 months these increased to over 70%. Those patients who switched to TNFis had initial response rates below 50% and response rates did not increase to 70% until 10 months.

11.4.1.3.4 Achieving DAS28 Scores Of 2.6 Or Less

A. Time To Achieve DAS28 Scores Of 2.6 Or Less

The time taken to achieve remission (DAS28 ≤2.6) was compared using Kaplan Meier plots. These results are shown in Figure 16. 36/104 (35%) of patients randomised to receive

cDMARDs and 44/101 (44%) of patients randomised to receive TNFis achieved remission at any time. There was no evidence that the speed of onset of remission was significantly different between groups (p=0.085). Those patients randomised to receive both cDMARDs and also TNFis who had DAS28 remissions achieved them within a mean of 4 months.

B. Persistence Of DAS28 Scores OF 2.6 Or Less

There was a complex pattern of achieving remission. In some patients remissions were persistent and in others they were unsustained. Examples of these variations are shown for 4 patients randomised to the TNFi group in Figure 17. As a consequence of these variations we have also evaluated the frequencies of responses each month, which are shown in Figure 19. There was a different pattern of responses between groups. Patients randomised to cDMARDs showed a gradual increase in the rate of responses from 5% or less at 3 months or earlier to a maximum of 20% by 12 months. By contrast, those patients randomised to TNFi had achieved a remission rate of 16% by 3 months, which gradually increased to a maximum of 32% by 11 months.

C. Impact Of Switching cDMARDs to TNFis

There was a difference in the patients randomised to cDMARDs who remained on cDMARDs and those who switched to TNFis. This is shown in Figure 18. In both groups fewer than 10% of patients achieved DAS28 scores of $\leq$2.6 at 5 months or less. Between 13% and 26% of patients remaining on cDMARDs achieved such low DAS28 scores from 6 to 12 months. Between 5% and 21% of patients who switched to TNFis had such low DAS28 scores between 6 and 12 months.

Figure 12: Kaplan Meier Plot of Time To Achieve Response (Reduction In DAS28 Score Of ≥1.2) Using All Observed Data

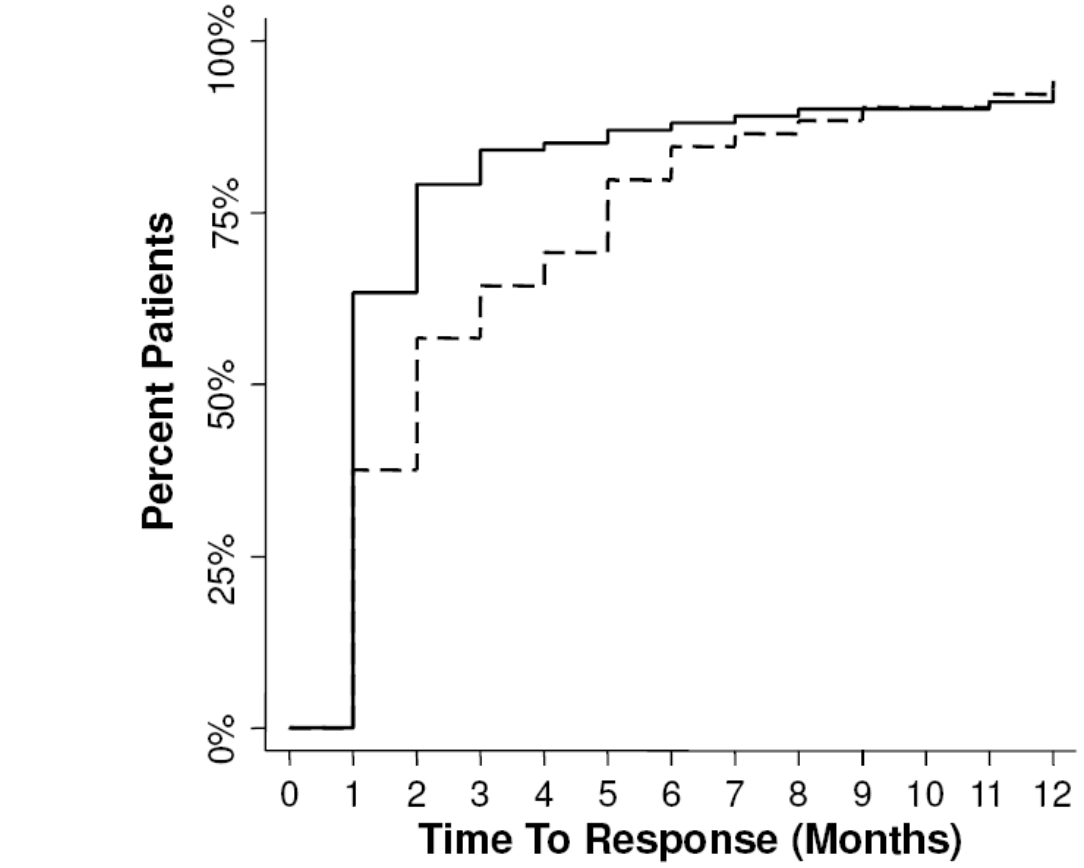


Figure 13: Examples Of Persistent And Unsustained Responses In Four Patients Randomised To TNFi Group

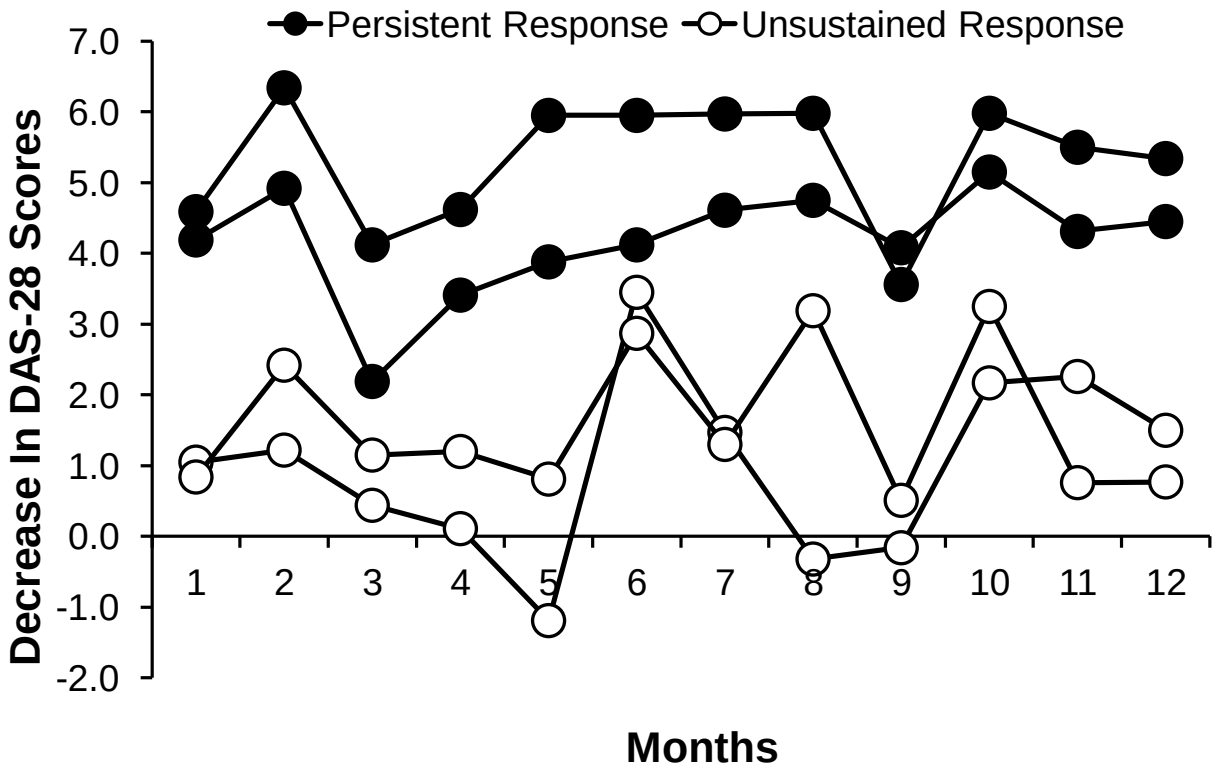


Figure 14: Frequency Of Response (Reductions In DAS28 Score ≥1.2) Each Month Using All Observed Data

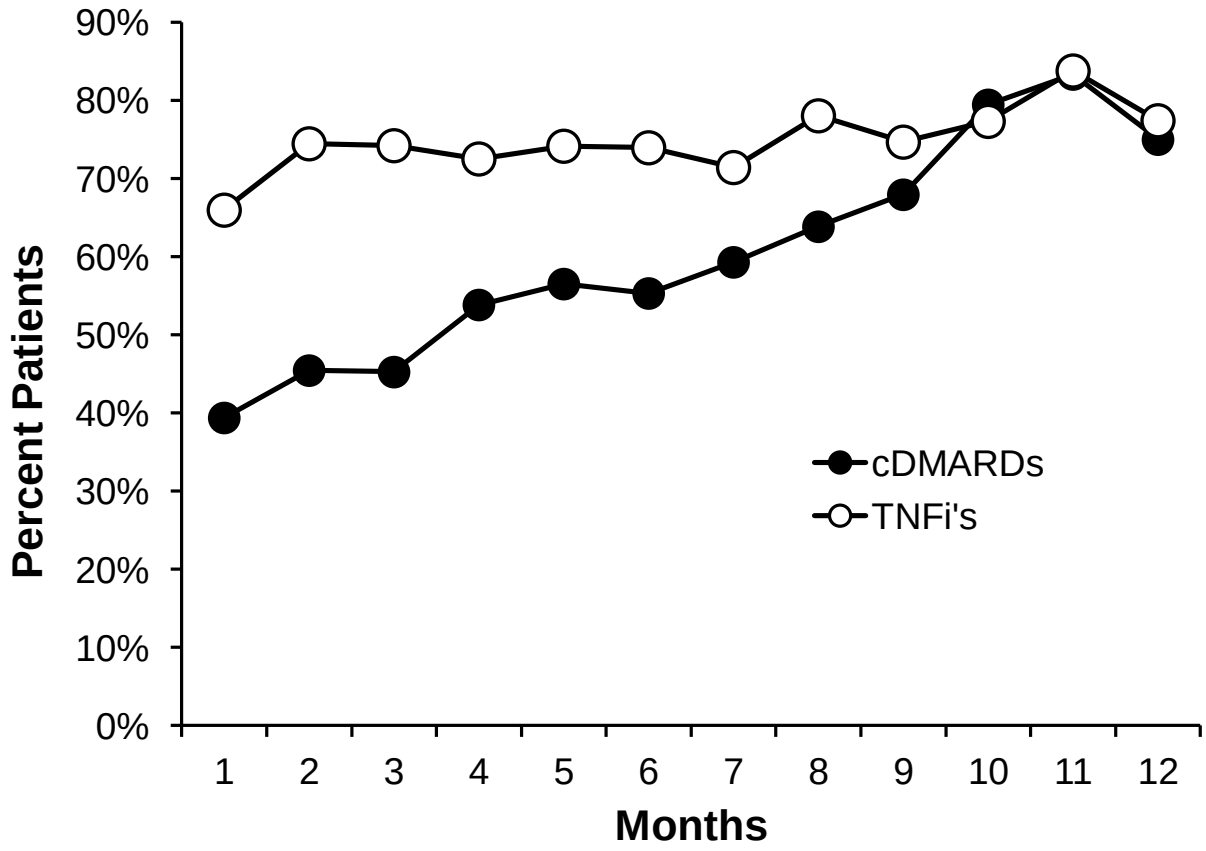


Figure 15: Frequency Of Response (Reductions In DAS28 Score ≥1.2) Each Month In Patients In cDMARD Arm Who Remained On cDMARDs Or Switched To TNFI's. Using All Observed Data

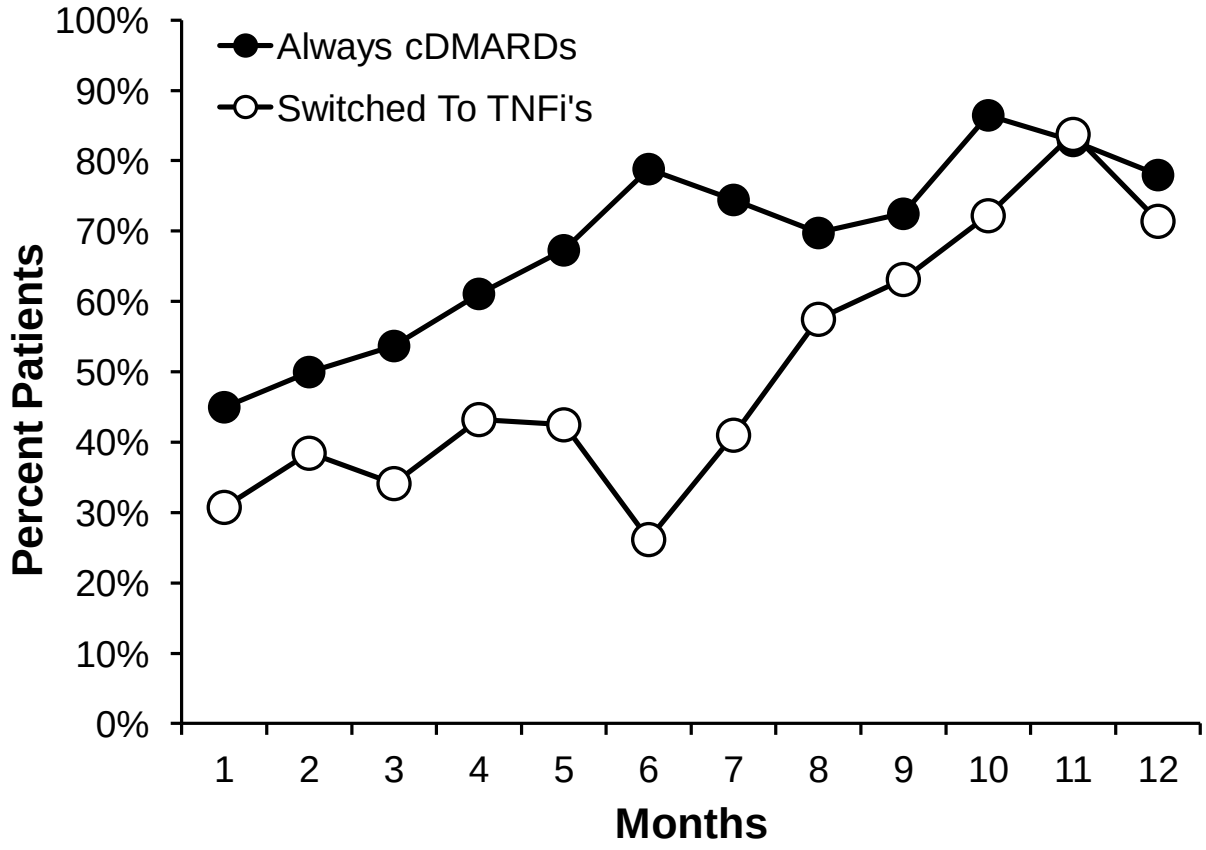


Figure 16: Kaplan Meier Plot of Time To Achieve DAS28 Remission (Score Of ≤2.6) Using All Observed Data

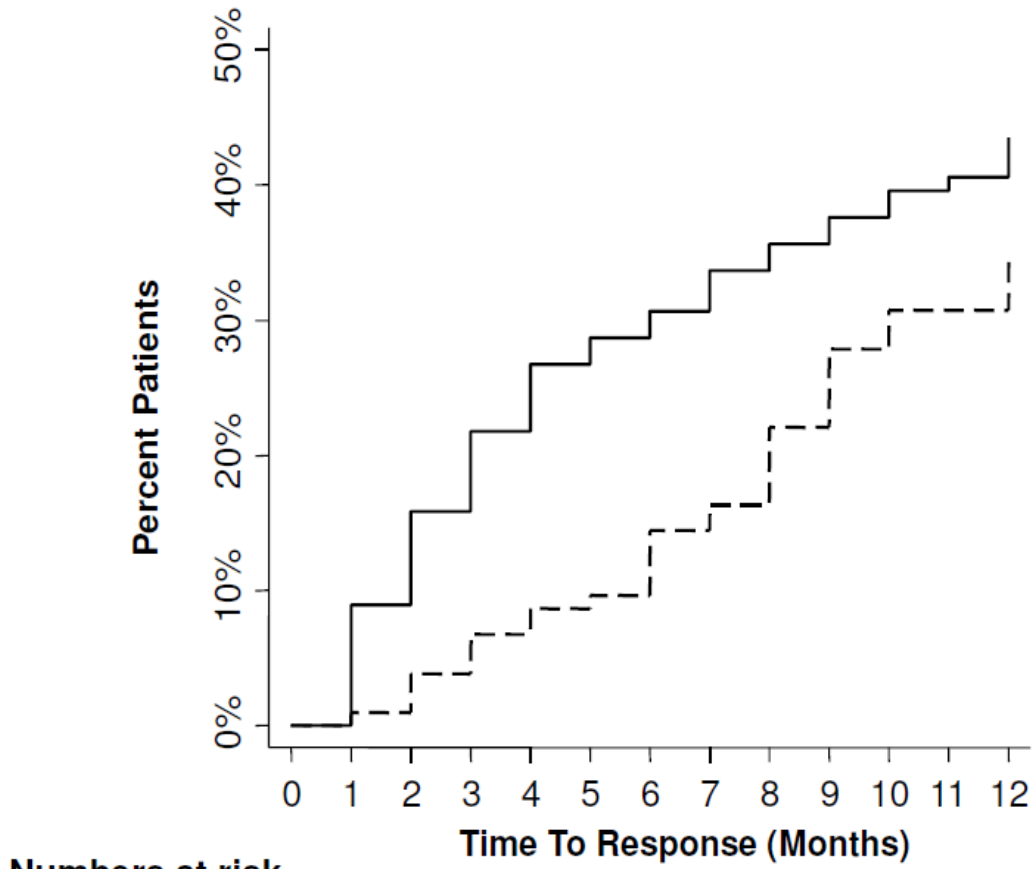


Figure 17: Examples Of Persistent And Unsustained Remission In Four Patients Randomised To TNFi Group

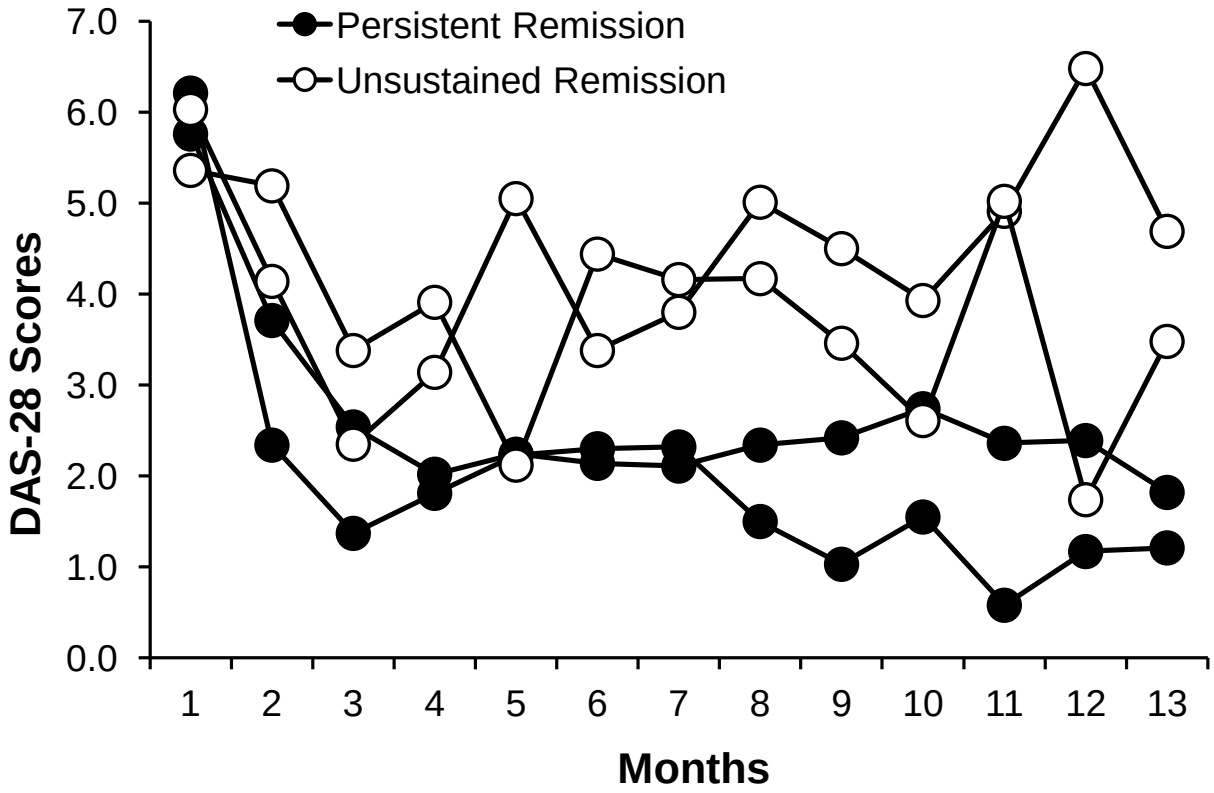


Figure 18: Frequency Of DAS28 Remission (Score Of ≤2.6) Each Month Using All Observed Data

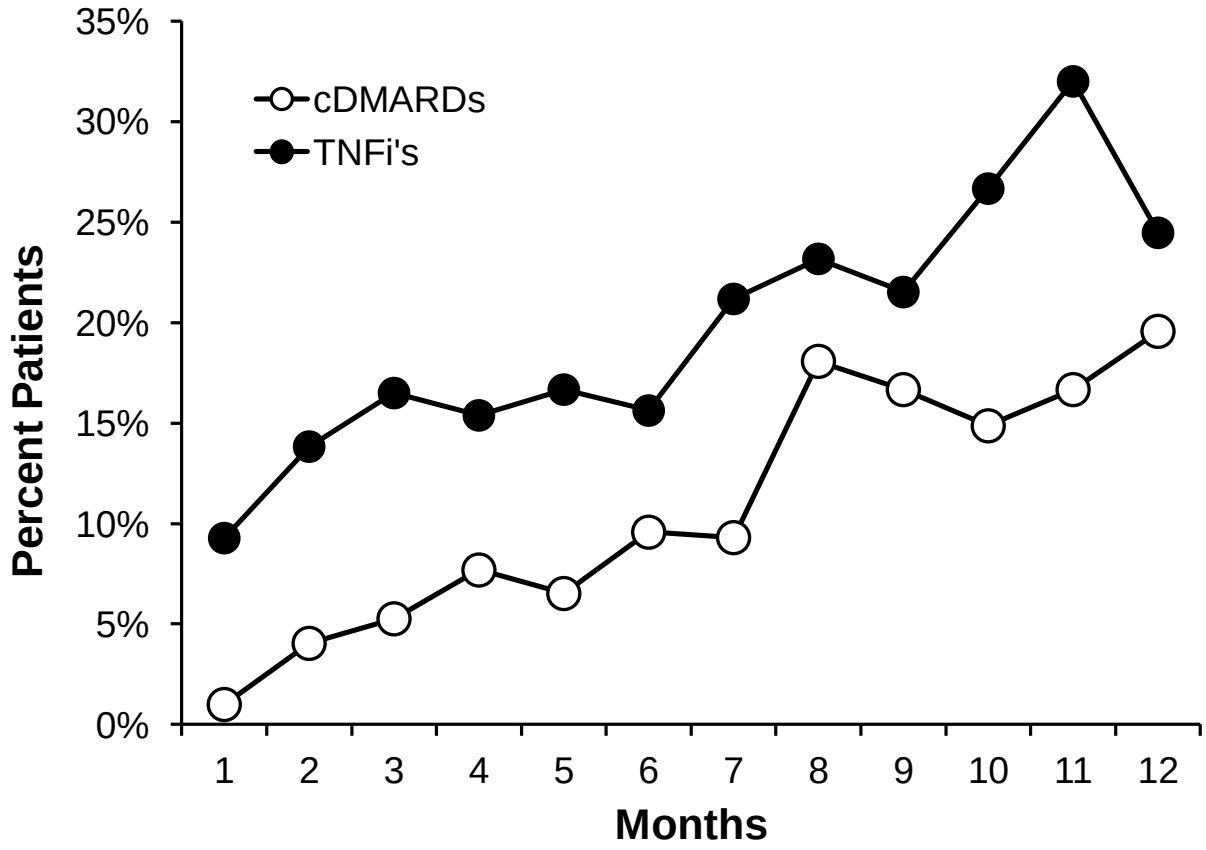
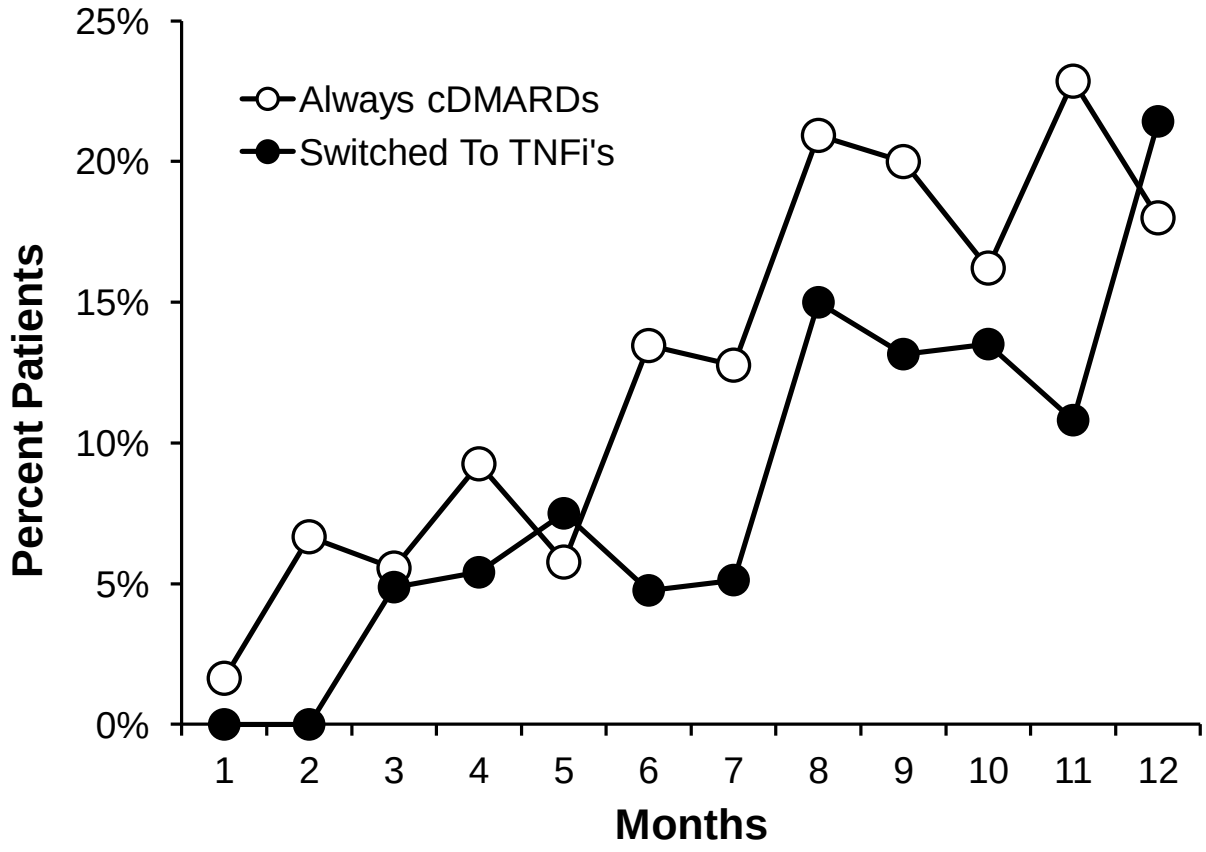


Figure 19: Frequency Of DAS28 Remission (Score Of ≤2.6) Each Month In Patients In cDMARD Arm Who Remained On cDMARDs Or Switched To TNFI's. Assessed Using All Observed Data



11.4.2 Economic Evaluation

11.4.2.1 Response Rates

The response rates for the CSRI, outcome questionnaires and trial medication data are summarised in Tables 16 to 18. These were above 90% and similar for all questionnaires at baseline, 6 and 12 months and across both trial arms.

Table 19 summarises the joint availability of both cost and outcome data (a requirement for the constructions of CEACs), by outcome measure. 191 (93%) of the 205 study participants had both cost and outcome data at 6 month follow-up. 186-188 (91-92%) of the 205 study participants had both cost and outcome data at 12 month follow-up. There were thus very few cases excluded from the available case analyses.

Tables 20 to 22 suggest there were no notable differences in the characteristics of the sub-samples included in the available case analyses and the full sample.

Table 16: Client Service Receipt Inventory (CSRI) Response Rates

	Baseline		**6 months**		**12 months**	
	n	***%***	***n***	***%***	***n***	***%***
TNFi (n=101)	101	100	97	96	93	92
cDMARD (n=104)	104	100	94	90	95	91
Total (n= 205)	205	100	191	93	188	92

Table 17: Health Assessment Questionnaire, EQ5D And SF-36 Response Rates

Outcome	**Group**	**Baseline**		**6 months**		**12 months**	
		n	*%*	*n*	*%*	*n*	*%*
HAQ	TNFi (n=101)	101	100	97	96	94	93
	cDMARD (n=104)	104	100	94	90	95	91
	Total (n=205)	205	100	191	93	189	92
EQ-5D	TNFi (n=101)	101	100	97	96	93	92
	cDMARD (n=104)	104	100	94	90	94	90
	Total (n=205)	205	100	191	93	187	91
SF-36	TNFi (n=101)	101	100	97	96	94	93
	cDMARD (n=104)	104	100	94	90	95	91
	Total (n=205)	205	100	191	93	189	92

Table 18: Availability Of Trial Medication Data

Group	**6 months**		**12 months**	
	n	*%*	*n*	*%*
TNFi (n=101)	97	96	94	93
cDMARD (n=104)	97	93	96	92
Total (n= 205)	194	95	190	93

Table 19: Availability Of Both Cost And Outcome Data, By Outcome Measure

Outcome	**Group**	**6 months**		**12 months**	
		n	***%***	***n***	***%***
HAQ	TNFi (n=101)	97	96	93	92
	cDMARD (n=104)	94	90	95	91
	Total (n=205)	191	93	188	92
EQ-5D	TNFi (n=101)	97	96	92	91
	cDMARD (n=104)	94	90	94	90
	Total (n=205)	191	93	186	91
SF-36	TNFi (n=101)	97	96	93	92
	cDMARD (n=104)	94	90	95	91
	Total (n=205)	191	93	188	92

Table 20: Characteristics Of Full Sample And Sub-Sample With Costs And HAQ

	Full sample		**Sub-sample with 6month cost and HAQ data**		**Sub-sample with 12 month cost and HAQ data**	
	(n=205)		*(n=191)*		*(n=188)*	
	n	*%*	*n*	*%*	*n*	*%*
Gender:						
Male	53	26	45	24	46	25
Female	152	74	146	76	142	76
Ethnicity:						
White	181	88	168	88	164	87
Other	24	12	23	12	24	13
Region:						
London & South	128	62	127	67	121	64
Midlands	16	8	13	7	13	7
North	61	30	51	27	54	29
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
Age	57.34	11.97	57.11	11.94	56.91	12.02
Duration of illness in years	8.20	8.82	8.35	8.98	8.24	8.88
HAQ at baseline	1.85	0.63	1.86	0.63	1.85	0.64

Table 21: Characteristics Of Full Sample And Sub-Sample With Costs And EQ-5D

	Full sample *(n=205)*		**Sub-sample with 6month cost and EQ-5D data** *(n=191)*		**Sub-sample with 12 month cost and EQ-5D data** *(n=186)*	
	n	*%*	*n*	*%*	*n*	*%*
Gender:						
Male	53	26	45	24	45	24
Female	152	74	146	76	141	76
Ethnicity:						
White	181	88	168	88	162	87
Other	24	12	23	12	24	13
Region:						
London & South	128	62	127	67	121	65
Midlands	16	8	13	7	11	6
North	61	30	51	27	54	29
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
Age	57.34	11.97	57.11	11.94	56.84	12.08
Duration of illness in years	8.20	8.82	8.35	8.98	8.25	8.92
HAQ at baseline	1.85	0.63	1.86	0.63	1.85	0.64
EQ-5D based utility at baseline	0.37	0.31	0.37	0.31	0.37	0.31

Table 22: Characteristics Of Full Sample And Sub-Sample With Costs And SF-36

	Full sample *(n=205)*		**Sub-sample with 6month cost and EQ-5D data** *(n=191)*		**Sub-sample with 12 month cost and EQ-5D data** *(n=186)*	
	n	*%*	*n*	*%*	*n*	*%*
Gender:						
Male	53	26	45	24	46	25
Female	152	74	146	76	142	76
Ethnicity:						
White	181	88	168	88	164	87
Other	24	12	23	12	24	13
Region:						
London & South	128	62	127	67	121	64
Midlands	16	8	13	7	13	7
North	61	30	51	27	54	29
	Mean	*SD*	*Mean*	*SD*	*Mean*	*SD*
Age	57.34	11.97	57.11	11.94	56.91	12.02
Duration of illness in years	8.20	8.82	8.35	8.98	8.24	8.88
HAQ at baseline	1.85	0.63	1.86	0.63	1.85	0.64
SF-36 based utility at baseline	0.54	0.11	0.54	0.11	0.54	0.11

11.4.2.2 Resource Use

Resource use differences were not compared statistically, firstly because the economic evaluation was focused on costs and cost-effectiveness/utility and, secondly, to avoid problems associated with multiple testing. Therefore, resource use patterns are described in Tables 23 to 25 without statistical comparisons. Use of services appeared similar in both the TNFi and cDMARD groups at all three time points. General practitioner surgery visits, practice nurse surgery visits, repeat prescription requests and hospital outpatient appointments were common in both groups at all time points, with other service use being relatively rare. The number of participants using non-trial medications was also similar in both groups at all time points.

Data on the use of NHS/Social Service-funded equipment and transport (costs of which are excluded from cost calculations) are presented in Table 26**.**

Table 23: Resource Use At Baseline (In Previous 3 Months)

	Unit	**cDMARD (n=94)**			**TNFi (n=97)**		
		Number of users	*Mean**	*SD*	*Number of users*	*Mean**	*SD*
GP							
At surgery	Visit	70	2	2	73	3	2
At home	Visit	3	1	1	3	1	1
Phone call	Call	16	2	1	15	2	1
Repeat prescription request without GP contact	Prescription	93	3	2	92	3	2
Nurse							
At surgery	Visit	42	3	4	50	2	2
Phone call	Call	6	1	<1	7	1	<1
Physiotherapist							
At hospital	Unit	7	2	2	9	2	1
At home	Visit	0	-	-	1	3	-
At GP surgery	Visit	2	11	13	1	3	-
Elsewhere	Visit	0	-	-	0	-	-
Occupational therapist							
At hospital	Unit	5	4	5	5	1	1
At home	Visit	3	2	1	5	1	1
At GP surgery	Visit	0	-	-	0	-	-

Elsewhere	Visit	0	-	-	2	2	<1
Hospital services							
A&E	Unit	9	1	<1	6	1	<1
Hospital stay overnight	Night	4	2	1	3	12	6
Outpatient appointment	Unit	77	3	2	85	3	2
Social services							
Meals on wheels	Meal	0	-	-	0	-	-
Home help	Visit	0	-	-	1	90	-
Social worker	Hour	0	-	-	2	3	1
Social worker phone call	Call	0	-	-	3	1	<1
Other health or social service	Contact	1	1	<1	4	3	2
Non-trial medication	Medication	102	-	-	100	-	-

*Mean for users only

Table 24: Resource Use At 6 Month Follow-Up (In Previous 3 Months)

	Unit	**cDMARD (n=94)**			**TNFi (n=97)**		
		Number of users	*Mean**	*SD*	*Number of users*	*Mean**	*SD*
GP							
At surgery	Visit	42	2	1	55	2	1
At home	Visit	2	1	<1	3	2	1
Phone call	Call	9	2	1	14	1	1
Repeat prescription request without GP contact	Prescription	63	3	1	70	3	1
Nurse							
At surgery	Visit	31	3	3	31	3	4
Phone call	Call	2	2	1	2	1	<1
Physiotherapist							
At hospital	Unit	8	4	3	4	3	1
At home	Visit	0	-	-	0	-	-
At GP surgery	Visit	2	3	<1	1	1	-
Elsewhere	Visit	0	-	-	2	2	1
Occupational therapist							
At hospital	Unit	4	2	1	3	1	1
At home	Visit	2	1	<1	4	1	<1
At GP surgery	Visit	0	-	-	0	-	-

Elsewhere	Visit	1	1	-	0	-	-
Hospital services							
A&E	Unit	4	1	<1	9	1	<1
Hospital stay overnight	Unit / night	4	4	5	5	7	5
Outpatient appointment	Unit	55	3	2	58	3	1
Social services							
Meals on wheels	Meal	1	60	-	0	-	-
Home help	Visit	1	1	-	2	46	63
Social worker	Hour	3	1	1	3	1	1
Social worker phone call	Call	1	2	-	1	3	-
Other health or social service	Contact	3	31	51	3	14	11
Non-trial medication	Medication	88	-	-	94	-	-

*Mean for users only

Table 25: Resource Use At 12 Month Follow-Up (In Previous 3 Months)

	Unit	**cDMARD (n=104)**			**TNFi (n=101)**		
		Number of users	*Mean**	*SD*	*Number of users*	*Mean**	*SD*
GP							
At surgery	Visit	60	2	1	58	2	2
At home	Visit	4	2	1	3	1	1
Phone call	Call	16	1	1	13	1	1
Repeat prescription request without GP contact	Prescription	68	3	2	61	2	1
Nurse							
At surgery	Visit	24	2	1	31	2	2
Phone call	Call	2	1	<1	5	2	1
Physiotherapist							
At hospital	Unit	11	5	6	7	3	2
At home	Visit	0	-	-	0	-	-
At GP surgery	Visit	1	8	-	2	3	3
Elsewhere	Visit	1	1	-	1	2	-
Occupational therapist							
At hospital	Unit	6	2	1	1	1	-
At home	Visit	1	1	-	1	1	-
At GP surgery	Visit	0	-	-	0	-	-

Elsewhere	Visit	1	1	-	1	3	-
Hospital services							
A&E	Unit	10	1	<1	5	1	1
Hospital stay overnight	Unit / night	5	2	1	2	11	13
Outpatient appointment	Unit	56	2	1	55	3	2
Social services							
Meals on wheels	Meal	0	-	-	0	-	-
Home help	Visit	0	-	-	3	31	51
Social worker	Hour	1	1	-	2	2	<1
Social worker phone call	Call	2	2	1	1	1	-
Other health or social service	Service	2	19	16	2	1	<1
Non-trial medication	Contact	90	-	-	91	-	-

Table 26: Use of NHS/Social Services transport, equipment and home adaptations at baseline, 6 and 12 months

	cDMARDs			***TNFi***		
	Number of users/ Total number	*Number paid by NHS*	*Number paid by social services*	*Number of users/ Total number*	*Number paid by NHS*	*Number paid by social services*
Baseline						
Transport	5/104	4	1	3/101	2	1
Equipment	4/104	1	3	2/101	0	2
Home adaptations	4/104	1	3	1/101	0	1
Other	2/104	1	1	3/101	1	2
6 months						
Transport	6/94	6	0	4/97	3	1
Equipment	2/94	0	2	4/97	0	4
Home adaptations	4/94	2	2	3/97	0	3
Other	0/94	0	0	2/97	0	2
12 months						
Transport	2/95	2	0	6/93	6	0
Equipment	3/95	1	2	2/93	0	2
Home adaptations	1/95	1	0	3/93	0	3
Other	1/95	0	1	1/93	0	1

11.4.2.3 Costs

Cost components at baseline, 6 months and 12 months are summarised in Table 27. Costs for both groups were equivalent at baseline. Costs of social security benefits and employment losses are small compared to the cost of health and social care. At 6 and 12 month follow-up, all cost components remained equivalent between groups, except for the cost of trial medications which were significantly lower in the cDMARDs group (6 month adjusted mean difference: -£3637, CI -£3838 to -£3420; 12 month adjusted mean difference: -£1894, CI -£2320 to -£1427). The additional trial medication costs in the TNFi group overshadowed all other cost components in that group.

The increase in trial medication costs in the cDMARDs group between 6 and 12 months was due to a significant proportion of this group switching to the more expensive TNFi inhibitors at 6 months due to non-response to cDMARDs by 6 months. Switching in the reverse direction was uncommon (total of 4 participants) so trial medication costs in the TNFi group did not fall a great deal between 6 and 12 months.

Table 28 shows total costs at 6 and 12 months from a health and social care perspective and the two societal perspectives we adopted (with and without social security benefit costs). All figures (including those for trial medications) represent a three-month period. The cDMARDs group have significantly lower total costs from all perspectives at both follow-up points. The difference is greater at 6 months than at 12 months due to the greater trial medication cost differential prior to switching taking place. Costs from each of the societal perspectives are similar to those from a health and social care perspective due to the dominance of trial medication costs.

For the purpose of combining cost and outcome data for the cost-effectiveness/utility analyses, all costs were equivalised to 6-month values. Trial medication costs were available for the 0-6 month and 7-12 month periods so all other costs were multiplied by two to represent 6-, rather than 3-month periods. Extrapolated figures are shown in Table 29. Imputing missing cost data (based on the extrapolated costs) for those lost to follow-up confirmed findings from the unimputed available case data (Table 30).

11.4.2.4 Outcomes

The cDMARDs arm had an advantage of 4 points on SF-36 based utility scores at baseline but this did not carry through as an advantage in (baseline-adjusted) utility scores at either of the two follow-ups or the resulting QALY estimates (Table 31). The cDMARDs group did however show advantages on the HAQ and EQ-5D based utility scores at 12 months, although the latter did not translate into advantages on QALYs estimated from the EQ-5D. As with cost data, imputing missing outcome data for those lost to follow-up did not alter conclusions from the available case analyses (Table 32).

11.4.2.5 Cost-Effectiveness And Cost-Utility Analyses

Table 33 summarises conclusions from comparisons of costs from each perspective (based on extrapolations representing 6-month periods) and outcomes at 6 and 12 months. Only one cost-outcome combination suggested that the cDMARDs group dominate the TNFi group (i.e. have better costs and outcomes): at 12 months, the cDMARDs group show significantly lower costs and significantly better HAQ scores. However, in all other cost-outcome combinations, the cDMARDs group suggest superiority with equivalent outcomes achieved at a significantly lower cost. Conclusions remain the same when costs and outcomes for those lost to follow-up were imputed. It was not necessary to compute any incremental cost-effectiveness ratios as none of the combinations suggested significantly better outcomes at significantly greater cost for one group compared with the other.

Table 27: Cost Components At Baseline, 6 And 12 Months

	TNFi n=101			cDMARD n=104			Unadjusted Difference[$]		Adjusted Difference[$$]	
	Valid n	*Mean £*	*SD*	*Valid n*	*Mean £*	*SD*	*Mean*	*95% CI*	*Mean*	*95% CI[$]*
Costs At Baseline										
Health & social care *Excluding trial medication***	101	736	1082	104	601	476	-131	-379 to 97	-	-
Employment losses**	101	60	262	104	84	440	24	-66 to 131	-	-
Social security benefits**	101	71	76	104	63	67	-9	-29 to 12	-	-
Costs At 6 Months										
Health & social care *Excluding trial medication***	97	536	947	94	511	705	-27	-262 to 202	6	-217 to 206
Employment losses**	97	71	405	94	35	310	-35	-127 to 67	-35	-115 to 59
Social security benefits**	97	77	75	94	74	77	-2	-21 to 21	3	-15 to 19
Trial medication***	97	4166	1012	97	510	356	-3660*	-3855 to -3432	-3637*	-3838 to -3420
Costs At 12 Months										
Health & social care *Excluding trial medication***	95	659	1699	93	583	634	-74	-486 to 255	-24	-363 to 230
Employment losses**	93	19	132	95	2	18	-16	-46 to 2	-17	-42 to 2

Social security benefits**	93	85	83	95	77	84	-6	-32 to 16	5	-12 to 23
Trial medication***	96	3546	1631	94	1547	1547	-1988*	-2458 to -1555	-1894*	-2320 to -1427

[$]Comparisons include a covariate for region

[$$]Comparisons include covariates for equivalent baseline cost, baseline HAQ, duration of illness, age, gender, region and ethnicity

* Statistically significant

**3-month costs, ***6-month costs

Note: Most expensive treatment is shown first

Table 28: Total Costs At 6 And 12 Months

	TNFi n=101			cDMARD n=104			Unadjusted Difference[$]		Adjusted Difference[$$]	
	Valid n	*Mean £*	*SD*	*Valid n*	*Mean £*	*SD*	*Mean*	*95% CI*	*Mean*	*95% CI*[$]
Costs At 6 Months										
Health & social perspective *Including trial medication*	97	2547	1083	94	793	703	-1757*	-2006 to -1500	-1708*	-1973 to -1483
Societal perspective *Including trial medication* *Excluding social security benefits*	97	2617	1145	94	828	791	-1793*	-2050 to -1519	-1742*	-2024 to -1506
Societal perspective *Including Trial Medication* *Including Social Security Benefits*	97	2694	1148	94	902	802	-1794*	-2055 to -1515	-1742*	-2023 to -1506
Costs At 12 Months										
Health & social perspective *Including trial medication*	93	[154] 1	1608	95	1493	1089	-907*	-1327 to -524	-817*	-1170 to -481
Societal perspective *Including trial medication* *Excluding social security benefits*	93	2430	1645	95	1494	1088	-924*	-1351 to -540	-840*	-1205 to -501

Societal perspective										
Including trial medication	93	2515	1637	95	1571	1100	-930*	-1363 to -541	-841*	-1200 to -508
Including social security benefits										

All costs are for a 3-month retrospective period for all cost components, including the trial medications.

[$] Comparisons include a covariate for region

[$$] Comparisons include covariates for equivalent baseline cost, baseline HAQ, duration of illness, age, gender, region and ethnicity

* Statistically significant

Note: Most expensive treatment is shown first

Table 29: Costs Extrapolated To 6 Month Period For The Cost Effective And Cost Utility Analyses

	TNFi n=101			**cDMARD n=104**			**Unadjusted difference[$]**		**Adjusted difference[$$]**	
	Valid n	*Mean £*	*SD*	*Valid n*	*Mean £*	*SD*	*Mean*	*95% CI*	*Mean*	*95% CI[$]*
Costs At 6 Months										
Health & social care perspective *Including trial medication*	97	5238	2093	94	1538	1393	-3703*	-4175 to -3199	-3615*	-4104 to -3182
Societal perspective *Including trial medication* *Excluding social security benefits*	97	5379	2236	94	1607	1569	-3774*	-4298 to -3230	-3683*	-4198 to -3195
Societal perspective *Including Trial Medication* *Including Social Security Benefits*	97	5533	2[154]	94	1755	1591	-3778*	-4303to -3230	-3684*	-4199 to -3194
Costs At 12 Months										
Health & social care perspective *Including trial medication*	93	4866	3147	95	2718	1890	-2129*	-2941 to -1417	-1930*	-2599 to -1301
Societal perspective *Including trial medication* *Excluding social security benefits*	93	4904	3218	95	2722	1890	-2162*	-2977 to -1449	-1974*	-2648 to -1334
Societal perspective	93	5073	3208	95	2876	1914	-2175*	-2991 to -	-	-2644 to -1338

Including trial medication	1465	1977*
Including social security benefits		

[$] Comparisons include a covariate for region

[$$] Comparisons include covariates for equivalent baseline cost, baseline HAQ, duration of illness, age, gender, region and ethnicity

*Statistically significant

Note: Most expensive treatment is shown first

Table 30: Costs Extrapolated To 6 Month Period For The Cost Effective And Cost Utility Analyses Based On Imputed Data

	TNFi n=101			**DMARDs n=104**			**Unadjusted difference[$]**		**Adjusted difference[$$]**	
	Valid n	*Mean £*	*SD*	*Valid n*	*Mean £*	*SD*	*Mean*	*95% CI*	*Mean*	*95% CI*
Costs At 6 Months**										
Health & social care perspective *Including trial medication*	101	5234	2052	104	1520	1329	-3717*	-4205 to -32556	-3615*	-4067 to -3198
Societal perspective *Including trial medication* *Excluding social security benefits*	101	5373	2192	104	1594	1496	-3780*	-4341 to -3288	-3688*	-4195 to -3232
Societal perspective *Including trial medication* *Including social security benefits*	101	5527	2197	104	1743	1518	-3784*	-4348 to -3298	-3691*	-4194 to -3246
Costs At 12 Months***										
Health & social care perspective *Including trial medication*	101	4874	3023	104	2729	1816	-2137*	-2838 to -1516	-1937*	-2612 to -1353
Societal perspective *Including trial medication* *Excluding social security benefits*	101	4910	3092	104	2728	1818	-2173*	-2895 to -1535	-1971*	-2648 to -1377
Societal perspective *Including trial medication*	101	5080	3082	104	2887	1840	-2182*	-2885 to -1543	-1976*	-2668 to -1368

Including social security benefits

[$] Comparisons include a covariate for region

[$$] Comparisons include covariates for equivalent baseline cost, baseline HAQ, duration of illness, age, gender, region and ethnicity

*Statistically significant

** Missing data at 6 months imputed from baseline HAQ, duration of illness, age, gender, region, ethnicity and trial arm as well as equivalent baseline costs.

*** Missing data at 12 months imputed from baseline the same variables plus equivalent 6 month costs.

Note: Most expensive treatment is shown first

Table 31: Outcomes At Baseline, 6 And 12 Months

	TNFis			cDMARDs			Unadjusted difference[$]		Adjusted difference[$$]	
	Valid n	***Mean***	***SD***	***Valid n***	***mean***	***SD***	***Mean***	***95% CI***	***Mean***	***95% CI***
Utilities and HAQ										
Baseline										
SF-36 utility	101	0.52	0.11	104	0.56	0.10	0.04*	0.01 to 0.07	-	-
EQ-5D utility	101	0.35	0.31	104	0.39	0.31	0.04	-0.04 to 0.12	-	-
HAQ	101	1.90	0.67	104	1.80	0.59	-0.10	-0.28 to 0.07	-	-
6 months										
SF-36 utility	97	0.59	0.13	94	0.62	0.12	0.03	-0.01 to 0.06	0.00	-0.03 to 0.03
EQ-5D utility	97	0.53	0.30	94	0.56	0.26	0.03	-0.05 to 0.10	-0.01	-0.08 to 0.06
HAQ	97	1.55	0.83	94	1.52	0.65	-0.03	-0.22 to 0.19	0.07	-0.08 to 0.21
12 months										
SF-36 utility	94	0.60	0.14	94	0.64	0.13	0.04*	0.01 to 0.08	0.03	-0.00 to 0.07
EQ-5D utility	93	0.50	0.31	94	0.60	0.28	0.10*	0.02 to 0.19	0.10	0.02 to 0.18*
HAQ	94	1.60	0.84	95	1.33	0.77	-0.27*	-0.51 to -0.04	-0.16*	-0.32 to -0.01
QALYs										
6 months										
SF-36 QALYs	97	0.28	0.05	94	0.30	0.05	0.02	0.00 to 0.03	0.00	-0.01 to 0.01

EQ-5D QALYs	97	0.22	0.14	94	0.24	0.12	0.02	-0.02 to 0.05	0.00	-0.02 to 0.02
12 months										
SF-36 QALYs	93	0.30	0.06	87	0.32	0.05	0.02	-0.00 to 0.03	0.01	-0.00 to 0.02
EQ-5D QALYs	92	0.26	0.13	88	0.29	0.11	0.03	-0.01 to 0.06	0.02	-0.01 to 0.05

[$]Comparisons include a covariate for region

[$]Comparisons of HAQ include covariates for baseline HAQ, duration of illness, age, gender, region and ethnicity; comparisons of utilities and QALYs include covariates for appropriate baseline utility, baseline HAQ, duration of illness, age, gender, region and ethnicity

*Statistically significant

Note: Most expensive treatment is shown first

Table 32: Outcomes For The Cost Effective And Cost Utility Analyses At 6 And 12 Months Based On Imputed Missing Data

	TNFis			cDMARDs			Adjusted difference[$]		Adjusted difference[$$]	
	Valid n	Mean	SD	Valid n	Mean	SD	Mean	95% CI	Mean	95% CI
6months										
HAQ**	101	1.55	0.82	104	1.51	0.64	-0.04	-0.24 to 0.16	0.07	-0.07 to 0.21
SF-36 QALYs***	101	0.28	0.05	104	0.29	0.05	0.02	0.00 to 0.03	0.00	-0.01 to 0.01
EQ-5D QALYs***	101	0.22	0.14	104	0.24	0.12	0.02	-0.02 to 0.05	-0.00	-0.02 to 0.02
12 months										
HAQ**	101	1.59	0.83	104	1.35	0.74	-0.25*	-0.45 to -0.03	-0.16*	-0.30 to -0.02
SF-36 QALYs***	101	0.30	0.06	104	0.32	0.06	0.02	0.00 to 0.03	0.01	-0.00 to 0.02
EQ-5D QALYs***	101	0.26	0.13	104	0.29	0.11	0.03	-0.00 to 0.06	0.02	-0.00 to 0.05

[$] Comparisons include covariate for region

[$$] Comparisons of HAQ include covariates for baseline HAQ, duration of illness, age, gender, region and ethnicity; comparisons of QALYs include covariates for appropriate baseline utility, baseline HAQ, duration of illness, age, gender, region and ethnicity

*Statistically significant

** Missing values at 6 month imputed based on baseline HAQ, duration of illness, age, gender, region, ethnicity and trial arm. Missing values at 12 months imputed based on the same predictors plus HAQ at 6 months.

*** Missing values at 6 months imputed based on baseline HAQ, duration of illness, age, gender, region, ethnicity, trial arm plus equivalent utility at baseline. Missing values at 12 months imputed based on the same predictors plus equivalent utility at 6 and 12 months.

Note: Most expensive treatment is shown first

Table 33: Cost-Effectiveness And Cost Utility Summary

	Cost per additional point improvement on the HAQ DMARDs vs TNFi	**Cost per additional QALY (SF-36based) DMARDs vs TNFi**	**Cost per additional QALY (EQ5D-based) DMARDs vs TNFi**
6 months			
Health & social care perspective	DMARDs same outcome, lower cost	DMARDs same outcome, lower cost	DMARDs same outcome, lower cost
Societal perspective excluding benefits	DMARDs same outcome, lower cost	DMARDs same outcome, lower cost	DMARDs same outcome, lower cost
Societal perspective including benefits	DMARDs same outcome, lower cost	DMARDs same outcome, lower cost	DMARDs same outcome, lower cost
12 months			
Health & social care perspective	DMARDs dominate with better outcome, lower cost	DMARDs same outcome, lower cost	DMARDs same outcome, lower cost
Societal perspective excluding benefits	DMARDs dominate with better outcome, lower cost	DMARDs same outcome, lower cost	DMARDs same outcome, lower cost
Societal perspective including benefits	DMARDs dominate with better outcome, lower cost	DMARDs same outcome, lower cost	DMARDs same outcome, lower cost

Incremental cost-effectiveness ratios only presented where one group has significantly greater benefit or a significantly greater cost

Figures 20 and 21 show the probability that the cDMARD group is cost-effective compared with the TNFi group for each outcome from a health and social care perspective at 6 and 12 months. Both EQ-5D and SF-36 based QALYs at each time point suggest that the probability that the cDMARD group is cost-effective is 99% or above at all willingness to pay thresholds that were examined.

The probability that the cDMARDs group is cost-effective at 6 months based on the HAQ is 100% for willingness to pay thresholds of up to £10,000 per point improvement on the HAQ but decreases at higher willingness to pay thresholds. At 12 months the probability of cost-effectiveness is 100% for willingness to pay thresholds of up to £10,000 per point improvement on the HAQ and remains at 99% up to a threshold of £50,000.

Figure 20: Cost-effectiveness acceptability curves for all outcomes at 6 months from a health and social care perspective

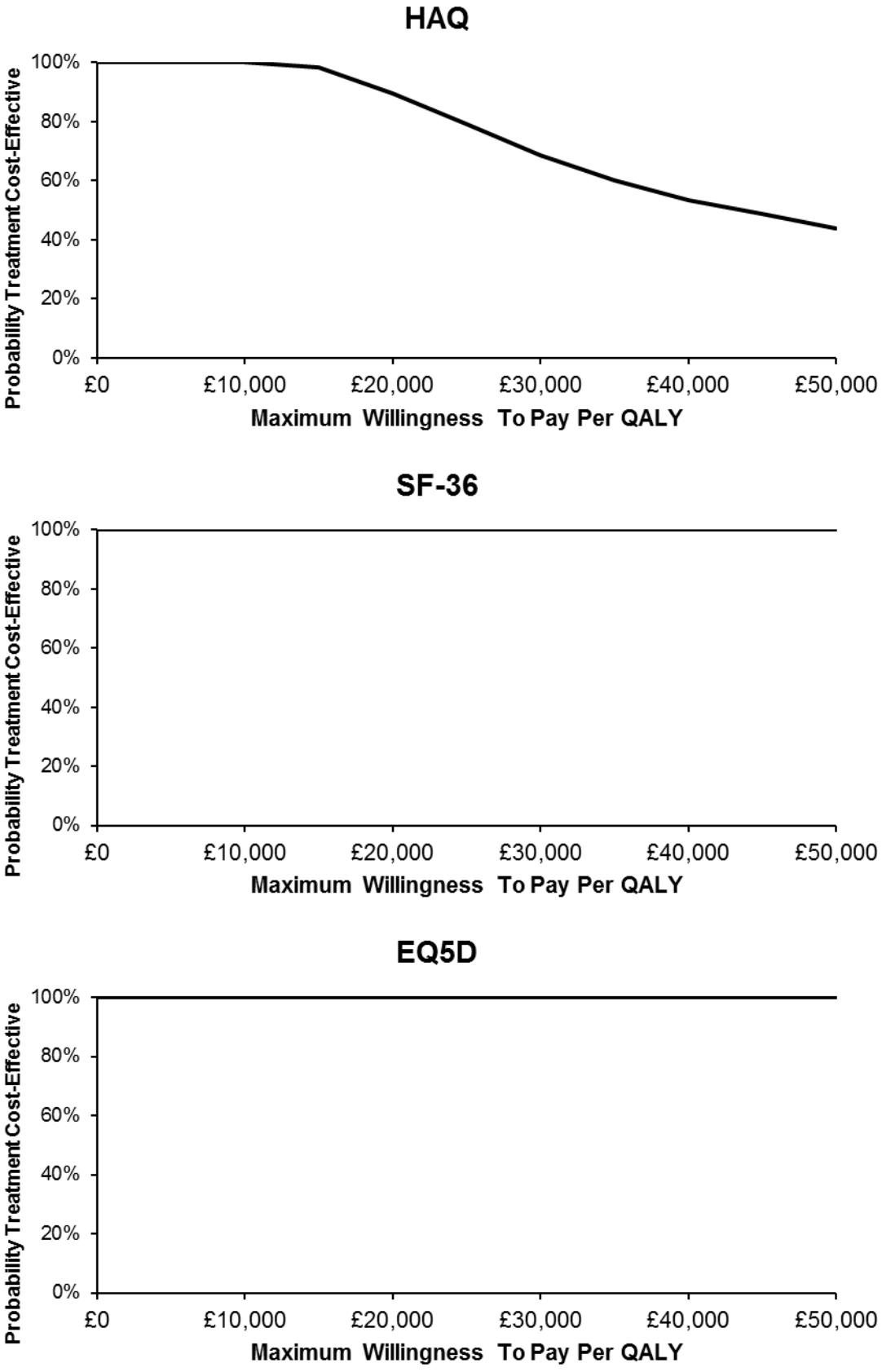
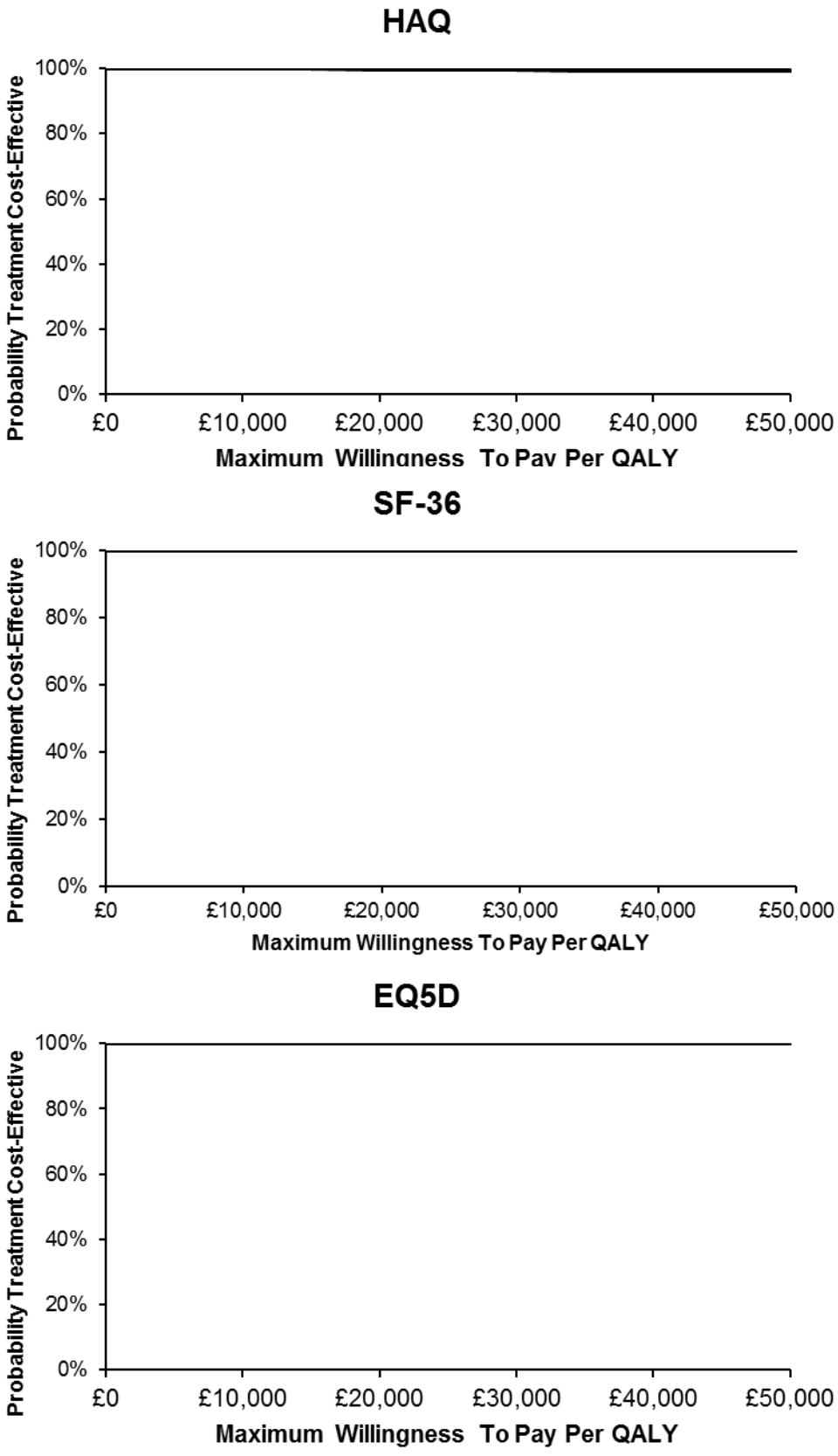


Figure 21: Cost-effectiveness acceptability curves for all outcomes at 12 months from a health and social care perspective



12.0 SAFETY EVALUATION

12.1 Serious Adverse Events

Ten patients in the cDMARD group had a serious adverse event; 8 in the first 6 months and 2 in the second 6 months (Table 34). Seven of these serious adverse events involved or prolonged inpatient treatment. 18 patients in the TNFi group had a serious adverse event; 6 in the first 6 months and 13 in the second 6 months. 13 of these serious adverse events involved or prolonged inpatient treatment. One patient in the TNFi group died during the second 6 months of treatment from pneumonia and multiple organ failure. Cardiovascular, respiratory, digestive and genitourinary systems were most commonly involved. Although there were more serious adverse events in the TNFi group, there was no evidence of major clinically important differences between the treatment groups and they frequency of adverse events was not significantly different (Fisher's exact test p=0.110).

12.1.1 Stopping Treatment Due To Adverse Events

This is described in the Consort Flowchart (Figure 1). 10 out of 104 patients (10%) in the cDMARD arm stopped treatment due to toxicity compared to 6 out of 101 (6%) in the TNFi arm. Although there more patients withdrew from treatment due to toxicity with cDMARDs, there was no evidence of major clinically important differences between the treatment groups and they frequency of withdrawals due to adverse events was not significantly different (Fisher's exact test p=0.441).

12.1.2 Individual Adverse Events

There were 635 different adverse events reported by patients in the cDMARD group. The most frequent events are listed in Table 18 and they are grouped by system involved in Table 35. All reported events are listed in Appendix 3 Table 1.

There were 465 different adverse events reported by patients in the TNFi group. The most frequent events are listed in Table 36 and they are grouped by system involved in Table 37. All reported events are listed in Appendix 3 Table 2.

Chest infections (46 events), headaches (45 events), diarrhoea (42 events), nausea (34 events), sore throats (28 events), colds (28 events), elevated liver enzymes (ALT) (23 events) and fatigue (16 events) were the commonest across both groups. Some types of adverse events spanned systems; in particular infections which accounted for 112 adverse events with cDMARDs and 117 with TNFis.

There was no evidence of any major clinically important differences between the two treatment groups. However, the cDMARD group had 36% more adverse events overall (635 vs 465): this difference was mainly due to 88 more adverse events in the digestive system with cDMARDs (148 vs 60) and 20 more in the nervous system (61 vs 41)

Table 34: All Serious Adverse Events

Adverse Events	**cDMARDs**			**TNFis**		
	0-6 Months	*6-12 Months*	*Total*	*0-6 Months*	*6-12 Months*	*Total*
Cardiovascular	2	0	2	1	1	2
Digestive	0	0	0	2	2	4
Ear, Nose, Throat	0	0	0	0	1	1
Endocrine/Metabolic	0	0	0	1	0	1
Genitourinary	3	0	3	0	1	1
Haematological	1	0	1	0	1	1
Mental	0	0	0	0	0	0
Musculoskeletal	0	0	0	0	1	1
Nervous System	0	1	1	1	1	2
Ophthalmological	0	0	0	0	0	0
Respiratory	2	1	3	1	3	3
Skin	0	0	0	0	2	2
Patient Died	0	0	0	0	1	1
Involved/Prolonged Inpatient Hospitalisation	5	2	7	5	8	13
Life Threatening	1	0	1	0	1	1

Table 35: Commonest Adverse Events (>1% Total Events)

cDMARDs			**TNFis**		
Adverse Reaction	*Number*	*Percent Total Reactions*	*Adverse Reaction*	*Number*	*Percent Total Reactions*
Diarrhoea	30	4.7%	Chest infection	27	5.8%
Headache	30	4.7%	Cold	16	3.4%
Nausea	26	4.1%	Elevated ALT	16	3.4%
Vomiting	26	4.1%	Headache	15	3.2%
Chest infection	19	3.0%	Flare of rheumatoid arthritis	14	3.0%
Flare of rheumatoid arthritis	17	2.7%	Sore throat	13	2.8%
Sore throat	15	2.4%	Diarrhoea	12	2.6%
Cold	12	1.9%	Urinary tract infection	9	1.9%
Ulcers - mouth	12	1.9%	Nausea	8	1.7%
Fatigue	11	1.7%	Breathlessness	7	1.5%
Dizziness	9	1.4%	Cold sore	7	1.5%
Elevated ALT	7	1.1%	Shoulder Pain	6	1.3%
Flu	7	1.1%	Upper respiratory tract infection	6	1.3%
High blood pressure	7	1.1%	Chest pain	5	1.1%
Itchy skin	7	1.1%	Cough - productive	5	1.1%
Low white cell count	7	1.1%	Fatigue	5	1.1%
			Injection site reaction	5	1.1%
			Vaginal Thrush	5	1.1%
			Knee Pain	5	1.1%

Table 36: All Adverse Events

Adverse Events	**cDMARDs**	**TNFis**
Cardiovascular	22	17
Digestive	148	60
Ear, Nose, Throat	88	76
Endocrine/Metabolic	7	7
Genitourinary	28	27
Haematological	25	10
Mental	24	15
Musculoskeletal	104	94
Nervous System	61	41
Ophthalmological	12	5
Respiratory	59	66
Skin	57	47
Total	*635*	*465*

13. DISCUSSION

13.1 Clinical Evaluation

13.1.1 Key Findings

Patients with active established RA who meet current NICE criteria to receive TNFis achieve equivalent reductions in disability and improvements in quality of life over 12 months by treating initially with cDMARDs and reserving TNFis for cDMARD non-responders. The cDMARD strategy cost substantially less. However, neither treatment strategy was ideal. The majority of patients in both groups failed to achieve DAS28 scores of 2.6 or less, which are often considered to indicate remission.

DAS28 scores improved more rapidly in patients receiving TNFis. Overall monthly DAS28 scores were lower with TNFis and more patients achieved DAS28 responses (decreases in score of 1.2 or more) within the first 6 months. This benefit of TNFis on DAS28 responses particularly reflected rapid and sustained reductions in the ESR in this group. However, the benefits of TNFis on DAS28 were small and did not result in improved disability or quality of life. There was also no evidence that patients who received cDMARDs had more erosive progression. Larsen scores showed both groups had comparable, minimal, x-ray progression.

The frequency of serious adverse events and withdrawals due to toxicity was similar with cDMARDs and TNFis. However, cDMARDs resulted in more overall adverse reactions, particular reactions involving the digestive system.

As TNFis are more expensive than cDMARDs, the economic evaluation showed the cDMARD group was overall substantially more cost-effective whatever approach was taken to assessing costs and relevant outcomes. This included incorporating societal costs such as lost time from work and social security benefit claims into the calculations.

Forty four percent of the [patients in the cDMARD group were recommended to switch to a TNFi because their disease activity had not improved after 6 months treatment. However, there was no evidence that patients who switched in this way had worse quality of life, more disability or more erosive progression. There was therefore no evidence that these “switchers” had any long term disadvantage from taking cDMARDs for 6 months.

13.1.2 Limitations And Sources Of Bias

Not all patients invited to participate agreed to do so; overall 192 out of 432 (44%) of patients declined to take part. We cannot be certain that the patients who did not consent to the trial would have responded in the same way as those who took part [149]. However, this is only one of a number of causes of bias in trials of long-term diseases [150] and does not seem a crucial factor when compared to the range of issues influencing such trials. In addition, patient choice is of crucial importance and accepting that not everyone will agree to participate is an inevitable consequence of informed choice around clinical trials. In addition, as discussed below, TACIT patients receiving TNFis were similar to those in the UK national register.

Those patients who did not respond to cDMARDs in TACIT were treated with TNFis. It could therefore be argued that the two arms of the trial end up being identical. Whilst a substantial proportion of patients did not persist with cDMARDs, and 44% of patients switched to TNFis in the second 6 months, the two trial arms remained sufficiently different to make this a genuine comparison. Furthermore the 6 month comparisons did not include any patients randomised to cDMARDs who had received TNFis (because no-one switched until after 6 months) and so there is a genuine head-to-head comparison within TACIT.

The cDMARD treatment was not standardised and it could be argued that the therapy given was too heterogeneous making it an intervention which could be difficult to reproduce. This is an intellectual challenge as the only way to standardise cDMARDs is to study early RA patients who are DMARD naïve or to study methotrexate non-responders. These patients do not meet existing NICE criteria to receive TNFis. If anything the cDMARD treatments used were too conservative. We had hoped patients would receive more intensive treatment and more short-term steroids in the cDMARD arm. However, supervising clinicians and patients placed more emphasis on slowly changing treatment to limit toxicity rather that giving maximal dose therapy as soon as possible. With greater use of cDMARDs the treatment intensity may be changed. We also accept that some combinations may be more effective, though this could not be resolved in TACIT. More trials of different combination DMARDs would be needed to answer this question.

Steroid use in the cDMARD group, including intra-muscular injections, was less than anticipated when designing TACIT based on our previous experience with steroids in

established RA [151]. UK rheumatologists may have concerns about treating many patients with steroids due to adverse events. However, the relatively limited use of steroids would serve to reduce rather than magnify the impact of cDMARDs. More intensive steroids use could make cDMARD treatment even more effective.

It could be argued that the same results could have been obtained from starting another DMARD monotherapy and that the use of intensive DMARD combinations in TACIT was not needed. This is a theoretical rather than a practical issue as there is no reason to stop on DMARD and start another in active RA in the absence of adverse events. DMARDs often have long half-lives, particularly agents like leflunomide. Consequently washing out current DMARDs and then starting a new DMARD monotherapy has limitations for patients as well as being of limited interest as the toxicity of modern DMARDs used in combination is not excessive.

The use of DMARDs other than methotrexate in combination with TNFis could have reduced the efficacy of these treatments in some patients. However, to do otherwise would be to move away from current UK practice, in which a range of DMARDs are given with TNFis. There is some evidence supporting the use of these different DMARDs in combination, as shown in our systematic reviews.

The use of HAQ as the primary outcome might be viewed by some experts as being inappropriate as the opportunity to reverse HAQ scores decreases with increasing disease duration [152,153]. Whilst this is theoretically correct, both our groups showed clinically relevant reductions in HAQ scores over 12 months. In addition the disease duration of patients in TACIT (median durations below 6 years in both groups) was below that in the Phase III trials which have led to the approval of the different TNFis. Furthermore, the degree of reduction of HAQ in TACIT was similar to that reported in previous trials of biologics. In our view if TNFis do not substantially reduce HAQ scores compared to other treatments their potential clinical value is limited.

The economic analysis only used data from within the trial. It could be argued that long-term modelling may make a more convincing case for using biologics. This is a reasonable view and no doubt the TACIT data needs to be considered within the longer-term modelling framework adopted by others.

TACIT was not a blinded trial. It could be argued that being un-blinded influenced patients and clinicians to favour cDMARDs inappropriately. However, it was impractical to have a fully blinded treatment strategy involving multiple different drugs all of which need careful monitoring. Given the enthusiasm of most clinicians and most patients for receiving high cost biological treatment we consider that un-blinding would, if anything, benefit TNFis. The issue of blinding is related to a number of ethical matters, which are considered below.

13.1.3 Analytical Issues

TACIT was analysed on an intention to treat basis using multiple imputations and the primary outcome was compared using logistic regression methods. HAQ is a complex assessment and it does not invariably behave as a conventional numerical scale [154]. There are identical issues about the linearity of the scales of other key outcome measures including EQ5D and Larsen scores. As both trial arms gave very similar outcomes with HAQ, EQ5D and increases in Larsen scores there is little merit in such an argument. In addition the overwhelming balance of advice we received favoured the analytical method we preselected.

Not all the outcomes confirmed equivalence. Changes in DAS28 and the ESR favoured TNFis, particularly within the first 3-6 months. In part this reflects the rapid onset of responses with TNFis and the slow onset of response with DMARDs, which historically and, probably, more accurately used to be known as slow acting drugs. Most DMARDs only show maximal effects by 6 months.

13.1.4 Strengths of TACIT

TACIT was undertaken in outpatient rheumatology clinics in England in conditions which, as far as is possible within a clinical trial, mirrored routine practice. The patients enrolled were typical of those treated within England and included patients from a range of ethnicities and levels of deprivation. They are similar to those reported in the BSR Biologics Register [155]. The comparability between patients enrolled in the BSR Biologics Register and TACIT are shown in Table 37. As there is evidence the patients enrolled in the BSR Biologics Register has changed over time, data from all available years is shown. Patients in TACIT had similar initial scores and similar changes (in the TNFi group) to patients most recently enrolled in the BSR Biologics Register.

TACIT focussed on patient centred outcomes. We consider it vital for such patient-centred outcomes have a central place in clinical trials in RA. Changes in measures such as the ESR, whilst of interest to clinicians, are of limited value to patients. There are also concerns about the inter-observer reproducibility of assessing joint counts.

TACIT was of sufficient size to provide robust assessments of the changes in measures. In addition it showed benefits favouring cDMARD treatment; in other words cDMARDs give somewhat better outcomes than just achieving equivalence. Although we do not think the trial shows that cDMARDs are preferable, the chance of the conclusions being incorrect and that TNFis are actually better appears remote.

TACIT showed that only a minority of patients randomised to TNFis achieved DAS28 scores of 2.6 or less. cDMARDs also resulted in relatively few DAS28 scores of 2.6 or less. These low scores are often considered to reflect remission though, as discussed in the introduction, defining remission is an on-going challenge. The frequency of such "remission scores" in TACIT is similar to that reported by both the BSR Biologics Register [155] and other international registers of patients receiving TNFis in routine clinical practice [156-159]. This is shown in Table 38. In addition to achieving single low DAS28 scores below 2.6, few TACIT patients achieve sustained remissions. There is a need for more research on the nature and predictors of sustained low DAS28 scores and other indicators of remission; this problem lies outside our remit in TACIT.

Table 37: Comparison Of BSR Biologics Register Outcomes (2001-8) [155] with TACIT TNFi Patients

Outcome	**Time**	**BSR Biologics Register (By Year)**								**TACIT TNFi Cases**	
		2001	*2002*	*2003*	*2004*	*2005*	*2006*	*2007*	*2008*	*ITT*	*Completers*
Number		119	1206	2930	3138	1553	1056	782	432	101	75
Mean HAQ	Baseline	2.21	2.14	2.10	2.04	1.98	1.95	1.87	1.87	1.90	1.84
	6 month change	0.26	0.33	0.32	0.32	0.34	0.33	0.33	0.32	0.35	0.41
	12 month change	0.31	0.33	0.33	0.33	0.34	0.35	0.34	0.37	0.30	0.38
Mean DAS28	Baseline	6.77	6.75	6.67	6.56	6.51	6.41	6.34	6.38	6.30	6.28
	6 months change	2.08	2.20	2.17	2.33	2.33	2.29	2.26	2.31	2.07	2.35
	12 month change	2.03	2.33	2.35	2.41	2.46	2.38	2.46	2.32	2.41	2.84

Table 38: Comparison Of DAS28 Remission Rates At 6 And 12 Months In Registries Of RA Patients Receiving First TNFi

Registry	**BSRBR [155]**	**CORONA [243]**	**DANBIO [244]**	**DREAM [245]**	**GISEA [246]**	**RABBIT [247]**	**Average**	**TACIT**
Patients	*11216*	*326*	*1839*	*1531*	*591*	*775*	*16278*	*101*
6 Month DAS28 Remission	16%	27%	21%	27%	26%	-	18%	15%
12 Month DAS28 Remission	14%	35%	21%	-		16%	16%	23%

13.2 Economic Evaluation

13.2.1 Key Findings

The economic evaluation indicates that initiating treatment with cDMARDs produces similar HAQ and QALY outcomes at 6 months at a significantly lower cost (from all cost perspectives) as compared with initiating treatment with TNFis. By 12 months, the cDMARD approach additionally brings advantages on the HAQ (-0.16, 95% CI -0.32 to -0.01) although a difference of this size is not considered to be clinically significant so can thus be regarded as clinically similar to the TNFi approach. The cost advantage in the cDMARDs group is almost entirely due to cDMARD medications being cheaper than TNFis.

In the cDMARDs group, costs at 12 months are significantly larger than at 6 months due to the high proportion of that group that switched from cDMARDs to TNFi medication at 6 months. Given that there is produced no outcome disadvantage in the cDMARD arm at 6 or 12 months, there may be some merit in a strategy of initiating treatment on cDMARDs as it incurs lower costs for those who remain on that treatment and delays the additional costs associated with TNFis for those who will go on to switch.

These findings are likely to be robust due to the breadth of the cost perspectives taken and the individual-level nature of the data which represents the variation in the sample. A pragmatic trial design performed within NHS settings also makes the findings applicable to the NHS.

13.2.2 Limitations

The economic evaluation has one notable limitation. Taking a broader cost perspective and a multi-centre approach necessitated collating data by self-report questionnaires, which carries the risk of recall bias. We limited the recall period to 3 months to guard against recall inaccuracies but this then necessitated extrapolating cost data to represent a longer period. This approach may not accurately reflect any variations that may exist across the measured and non-measured periods. However, we did have data for trial medication use over the entire period of follow-up and any biases associated with recall of other resource use would be not be expected to impact on the findings given the dominance of trial medication costs. We also have no reason to believe that any such recall bias would differ by randomisation group.

13.2.3 Clinical Implications

This economic evaluation suggests that at 6 months and 12 months following randomisation, cDMARDs are a more cost-effective treatment approach for rheumatoid arthritis as the cDMARDs group achieved similar outcomes as the TNFi group at a significantly lower cost.

13.3 Concerns For Patients Entering This Trial

Apart from general concerns about randomisation, especially for individuals who do not perceive true equipoise between treatments, there was 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).

13.4 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 TACIT is therefore timely from the perspective of both patients and recruiting clinicians.

13.5 Informing Potential Participants Of Benefits And Risks

Potential participants were identified by rheumatologists and specialist nurses in routine clinics at participating centres. They received a brief summary of relevant information about the trial including key risks and benefits. Those patients who were interested received 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 was drawn up by the Investigators and patient representatives based on the analysis of risks and benefits in this application; advice was sought from the full trial patient representatives group and the Trial Steering Committee before submission to the relevant Research Ethics Committee.

13.6 Clinical Implications

13.6.1 General Implications

TNFis and other biological treatments have revolutionised the treatments of RA and other inflammatory immune disorders. TACIT underlines the need for patients to have on-going access to these treatments. There is no evidence in TACIT to indicate that TNFis do not have a crucial role in the treatment of RA.

13.6.2 Clinical Implications

Existing NICE guidance for the use of TNFis in active RA is based on extensive reviews by leading experts of randomised controlled trials. Most of these trials have evaluated TNFis against placebos. The rationale for using TNFis is mainly derived from extrapolating the results of these placebo-controlled trials in modelling studies which examine the health economic benefits of TNFis with the help of historical data from observational studies. Prior to TACIT there have been no head-to-head trials comparing TNFis in established RA against alternative effective treatments.

There have been three head-to-head trials of cDMARDs against TNFis in early RA. These trials all show that treatment strategies starting with cDMARDs or with TNFis give equivalent results over 12-24 months. As a consequence there is no strong indication to start TNFis in preference to cDMARDs in such early RA patients. Current NICE guidance, in our view, correctly recommends that cDMARDs are used in active early RA [72].

The balance of current evidence suggests that the key role of TNFis in RA is in active disease which is not fully controlled by DMARDs. Placebo-controlled trials have established the efficacy of TNFis. Observational studies in registries have confirmed their safety. However, neither approaches has identified how best to use them. We consider that defining their optimal use requires undertaking head-to-head trials of different treatment strategies. Although more than a decade has passed since their introduction, we still do not know their value as short-term tapered treatments or if they should be given to selected sub-sets of patients.

If TNFis were low-cost treatments there would be little concern about their optimal use. However, they are amongst the most expensive of those treatments which are used for

relatively common diseases. As a consequence the payers for healthcare wish to ensure that their use delivers true “value for money”.

If TNFis ensured that most patients with active RA who received them entered a period of sustained remission, there would be relatively little difficulty defending their widespread use. However, TACIT and all other trials and observational studies show that only a minority of patients with active RA who receive TNFis achieve sustained remissions.

TNFis are usually simple for patients to take, adverse events are relatively uncommon, and the onset of their effect is usually fairly rapid. Therefore if cost did not come into it most patients would probably prefer to take TNFis rather than try cDMARDs [160]. However, this is probably the wrong question to ask. As neither strategy in TACIT ensured most patients with active RA enter remission, the real need is to identify more effective and more cost effective treatment strategies.

TACIT therefore shows that the current approach to using TNFis in established RA, encapsulated within current NICE guidance, does not result in cost-effective outcomes. We do not consider that using cDMARDs followed by TNFis represents an ideal approach. Instead further research is needed to identify more effective treatment strategies. For the present it appears preferable to ensure patients with active established RA receive the most clinically and cost-effective treatment possible. From this perspective offering cDMARDs before TNFis appears appropriate and sensible.

The model of care used in TACIT assumed that all patients with active established RA should be offered similar treatment. Using this approach some patients achieved very good responses with TNFis, a slightly small number of patients achieved very good responses with cDMARDs, a few patients achieved very good responses when they had TNFis after failing to respond to cDMARDs and most patients had relatively poor responses to all treatments. Universal treatment strategies do not appear very effective. The most sensible approach would be to individualise care [161,162].

13.6.3 Research Implications

Most clinicians consider TNFis are highly effective treatments for active RA. Yet we have found them to be no better than intensive combination DMARDs for many patients. One reason for clinicians favouring them is their rapid onset of action. Another is that patient selection for early trials of biologics may have given them a greater apparent benefit than occurs in routine practice as the patients had worse disease than is currently the case [163]. In addition there is extensive evidence, at least in some countries, that patients starting biologics in clinical practice have far milder disease than those patients in the clinical trials [164-7], making the translation of research findings into practice recommendations particularly challenging.

TACIT was a strategy trial that required patients to attend outpatient clinics for monthly review and involved substantial efforts from both patients themselves and also from the rheumatologists and specialist nurses in the collaborating centres. Prior to the trial starting there were concerns about the ethics of asking patients to wait for biological treatments and whether or not patients would wish to participate. One important conclusion from TACIT is that comparative trials of high cost treatments are feasible in long-term disorders like RA. Patients and clinicians are willing to take part in such trials and when they are undertaken in routine clinic settings they can deliver results of potential clinical relevance.

TACIT involved giving patients intensive combination DMARD treatments which were organised by specialist nurses and supervised by rheumatologists. Although some training was provided in the specific organisation of the trial, this did not include detailed training about how to deliver intensive DMARD combinations. Nevertheless, specialist nurses achieved this without any difficulties being encountered. A second general conclusion therefore is that rheumatology specialist nurses have sufficiently high levels of clinical skills to deliver more intensive DMARD combination therapy than is currently the case.

Finally, the costs of undertaking TACIT merit consideration. The trial was funded by a substantial grant from the HTA, and without this grant it could not have been undertaken. However, the savings from prescribing TNFis within TACIT to patients who met the criteria for receiving theses biologics but received cheaper DMARDs meant that the overall cost of TACIT to the NHS was relatively small. Therefore we consider it is possible to undertake further strategy trials with high cost treatments like TNFis for minimal additional costs to the

NHS as a whole. Clearly, as the funding comes from different sources it is not directly interchangeable. However, it is reasonable to suggest that many more NHS patients receiving high cost biologics for arthritis could be enrolled in strategy trials like TACIT to help the NHS identify the most effective and cost-effective ways to use high cost treatments.

The TNFis used in TACIT and a number of other biological agents in RA are licensed within Europe and North America for treating active RA. The Phase II and Phase III development programme for these agents have all been funded by their manufacturers and have used broadly similar trial methods focussing on patients who have failed to respond to treatments like Methotrexate either remaining on this treatment or taking an additional biologic. Such trial designs are efficient in establishing whether or not the biologics are effective. However, the regulatory process does not involve head-to-head comparisons of biologics with effective standard treatments. It is likely that the widespread adoption of the current approach by regulatory agencies might have over-emphasised the benefits of biologics compared to other less expensive forms of treatment. Clearly this a complex issue as there is a balance between the complexity and duration of the regulatory process versus the need to obtain full information about the relative value of new treatments. In our view there are advantages in placing head-to-head trials with effective comparators at some point in the regulatory pathway, an assessment which has been made by others [168,169].

TNFis achieve rapid improvements in the ESR and other measures of disease activity compared to conventional DMARDs. Indeed some licensed DMARDs, such as ciclosporin, have little impact on the ESR. The use of composite measures to assess treatment response in RA, such as DAS28 and ACR Responders is likely, in our opinion, to unduly favour TNFis. Their impact on measures such as HAQ and EQ5D, which are more reflective of patients' overall status, is less marked. The development of the current assessment methods in clinical trials in RA, which dates back to the 1990s, is based on expert opinion rather than direct evidence. Whilst the approach is likely to reduce sample size in trials, it may favour some forms of treatment over others. One way of minimising this risk is to ensure that trials cover a wide range of measures. Using changes in some measures, such as DAS28, to model changes in other measures, such as HAQ and EQ5D, seems particularly inappropriate.

The economic case for using biologics like TNFis in RA depends on extrapolating the results of placebo-controlled trials and using historical data from observational cohorts of previously

treated patients. This approach involves two challenges. Firstly, it is difficult to be certain how non-biological treatments would affect RA patients over time. Many of the models assume they would not do well but there is limited evidence to support this view. Secondly, the data used for modelling is often historical and changes in the severity and natural history of treated RA may mean that this historical data has limited relevance to current patients. We consider that the economic rationale for using biological treatments should involve more emphasis on directly collected information from clinical trials and give less emphasis on theoretical modelling over long-time frames.

14 CONCLUSIONS

14.1 Key Finding

The TACIT trial showed that RA patients who have failed to respond to methotrexate and another DMARD show clinically important improvements over 12 months if initially treated with combination DMARDs reserving TNFis for non-responders to these combinations. These improvements were equivalent to those achieved by starting all patients on TNFis in line with current national NICE guidance. Current guidance no longer represents the optimal use of NHS resources. The costs of an approach focussed on using cDMARDs are in the region of half costs with TNFis. The equivalence of cDMARDs with TNFis was confirmed in systematic reviews of published trials in both early and established RA.

The current management strategy for using TNFis in active RA costs the NHS over £200M annually. If cDMARDs can be used to control active RA in some patients with active established RA, it is likely that the resulting financial savings could be used to develop more cost effective ways of treating RA, including innovative approaches for using TNFis. We therefore recommend new approaches are explored which will optimise the use of biologics such as TNFis in RA.

14.2 Healthcare Implications

The results from TACIT, considered together with the systematic reviews of previous trials of intensive combination DMARDs and TNFis in active early and established RA suggest the following points could be considered when considering treating RA patients with biologics:

1. To maximise clinical and cost-effectiveness patients with active established RA who have failed initial DMARD treatment should receive intensive cDMARD therapy prior to initiating TNFis. This approach will maximise current clinical effectiveness and cost-effectiveness. A 6-month period of combination DMARD therapy is sufficient to assess its effectiveness and there is no evidence patients have long-term disadvantage in terms of future disability, quality of life or joint damage, from taking DMARD combinations for 6 months, even if they fail to respond.
2. In active established RA, starting treatments with either cDMARDs or TNFis results in equivalent clinically relevant improvements in disability and quality of life over 12 months. Although TNFis achieve rapid early improvements in disease activity, these

improvements do not result in larger improvements in disability or quality of life. Radiological progression was minimal with both cDMARDs and TNFis.

3. Neither cDMARDs nor TNFis represent ideal treatments because few patients achieve sustained remissions with either of them. These treatments should not therefore be seen as an end in themselves. Instead they appear to be no more than one of a number of therapeutic options which will reduce disease activity in patients with very active disease; they are not approaches that will result in most patients achieving sustained remissions.

14.3 Research Implications

TACIT raises many questions as well as providing some answers. There are a number of research areas which need to be taken forward. The following issues appear particularly important:

1. Identifying predictors of response to cDMARDs and TNFis will enable a move towards individualised treatment. This is of crucial importance as some patients respond well to cDMARD whilst others respond well to TNFis and prospectively identifying potential good responders should optimise treatment outcomes. In essence there is a need to move away from the conventional “one size fits all” approach to more personalised clinical care. Research needs to focus on identifying predictors for responses to these different treatment approaches. One possible implication is that national guidance on treatment decisions for specific interventions given to individual patients may not represent the most effective way of planning to deliver care. Guidance might be most appropriate it is moved from the general to the specific.
2. We need to define the most effective ways of using current treatments including undertaking more strategy trials to examine novel ways of using high cost treatments. Examples include identifying the benefits of short courses of biologics in early RA, where the rapid effects of biologics may be beneficial and re-defining the optimal duration of TNFi treatment in established RA. Currently once started TNFis are continued if patients respond. However, this approach is based on custom and practice and has not been tested in clinical trials. TACIT suggests TNFis have dramatic immediate benefits but that as currently used their major improvements are present by two or three months and, thereafter, patients do not generally improve further. It is possible that short-term “induction therapy” might be particularly useful with these treatments. Such an approach would change the cost-base of using biologic treatments.

3. There should be a greater emphasis on head-to-head trials when defining the overall benefits of high cost treatments in RA. Extrapolating the results of short-term placebo controlled trials and using observational studies to model economic benefits are less helpful in determining treatment pathways. Only head-to-head trials of treatment strategies including economic analyses can help drive forward innovative, cost-effective treatment approaches with biologics. The results of TACIT do not indicate that there should be less overall use of TNFis; it only indicates that they are not being used in a highly effective manner.
4. A range of new non-biological treatments, particularly kinase inhibitors, are being developed for RA and some of these agents may soon be introduced into clinical practice. It is too early to judge the potential impact of these new treatments but it is likely that the treatment paradigm will change as a result. TACIT highlights the limitations of our current treatment paradigm and therefore strengthens the case for developing new approaches to disease management.

The biologics revolution following the introduction of TNFis into routine clinical practice has changed RA care and, in our view, has benefited patients substantially. Clinicians and patients were keen to have access to these treatments when they first became available. As with all new treatments this is likely to have resulted in a relative over-estimation of their clinical and economic benefits. Time and experience usually temper the initial enthusiasm for new treatments, and this is likely to be the case with biologics for RA during the next decade. Trials like TACIT should help modify previous potential over-enthusiasm for biologics in RA. However, the development of new agents is more likely to have a major impact, as novelty is a potent driver for changing behaviour. In our view it does not matter so much what drives change; the crucial point is to realise that some changes are needed.

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16 APPENDICES

16.1 Appendix 1 Health Economic Costs

16.2 Appendix 2 Complete Case Population Analysis

16.3 Appendix 3 Adverse Events

16.4 Appendix 4 Patient Information Sheet

16.4.1 Appendix 5 TACIT protocol and MREC approval and amendment letters

16.4.2 Appendix 6 Sample case report form

16.4.3 Appendix 7 Principal Investigators CVs

16.4.4 Appendix 8 Consent Form

16.4.5 Appendix 9 MREC approval of GP letter

16.5 Appendix 10 Statistical Analysis Plan (SAP)