Tumour necrosis factor inhibitors versus combination intensive therapy with conventional disease modifying anti-rheumatic drugs in established rheumatoid arthritis: TACIT non-inferiority randomised controlled trial

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ABSTRACT

OBJECTIVE
To determine whether intensive combinations of synthetic disease modifying drugs can achieve similar clinical benefits at lower costs to high cost biologics such as tumour necrosis factor inhibitors in patients with active rheumatoid arthritis resistant to initial methotrexate and other synthetic disease modifying drugs.

DESIGN
Open label pragmatic randomised multicentre two arm non-inferiority trial over 12 months.

SETTING
24 rheumatology clinics in England.

PARTICIPANTS
Patients with rheumatoid arthritis who were eligible for treatment with tumour necrosis factor inhibitors according to current English guidance were randomised to either the tumour necrosis factor inhibitor strategy or the combined disease modifying drug strategy.

INTERVENTIONS
Biologic strategy: start tumour necrosis factor inhibitor; second biologic in six month for non-responders. Alternative strategy: start combination of disease modifying drugs; start tumour necrosis factor inhibitors after six months in non-responders.

MAIN OUTCOME MEASURE
Primary outcome: reduction in disability at 12 months measured with patient recorded health assessment questionnaire (range 0.00–3.00) with a 0.22 non-inferiority margin for combination treatment versus the biologic strategy. Secondary outcomes: quality of life, joint damage, disease activity, adverse events, and costs. Intention to treat analysis used multiple imputation methods for missing data.

RESULTS
432 patients were screened; 107 were randomised to tumour necrosis factor inhibitors and 101 started taking; 107 were randomised to the combined drug strategy and 104 started taking the drugs. Initial assessments were similar; 16 patients were lost to follow-up (seven with the tumour necrosis factor inhibitor strategy, nine with the combined drug strategy); 42 discontinued the intervention but were followed-up (19 and 23, respectively). The primary outcome showed mean falls in scores on the health assessment questionnaire of −0.30 with the tumour necrosis factor inhibitor strategy and −0.45 with the alternative combined drug strategy. The difference between groups in unadjusted linear regression analysis favoured the alternative strategy of combined drugs. The mean difference was −0.14, and the 95% confidence interval (−0.29 to 0.01) was below the prespecified non-inferiority boundary of 0.22. Improvements at 12 months in secondary outcomes, including quality of life and erosive progression, were similar with both strategies. Initial reductions in disease activity were greater with the biologic strategy, but these differences did not persist beyond six months. Remission was seen in 72 patients (44 with biologic strategy; 36 with alternative strategy); 28 patients had serious adverse events (18 and 10, respectively); six and 10 patients, respectively, stopped treatment because of toxicity. The alternative strategy reduced health and social care costs per patient by £3615 (€4930, $5585) for months 0–6 and £1930 for months 6–12.

CONCLUSIONS
In patients with active rheumatoid arthritis who meet English criteria for biologics an alternative strategy with combinations of intensive synthetic disease modifying drugs gives non-inferior outcomes to treatment with tumour necrosis factor inhibitors. Costs are reduced substantially.

TRIAL REGISTRATION
ISRCTN 37438295.

Introduction
Tumour necrosis factor inhibitors, the first biologics for rheumatoid arthritis, have changed specialist
Disease modifying drug strategy

This had four steps:
- Maximise initial disease modifying drug treatment(s)
- Add second/third disease modifying drug
- Start fourth/fifth disease modifying drug
- Offer tumour necrosis factor inhibitors after six months if fall in disease activity score for 28 joints was <1.2.

Disease modifying drugs were given in combination and sequentially. Patients taking oral prednisolone at entry continued as needed; short term oral or intramuscular steroids were an option with this strategy.

Participants

Patients were recruited from 24 rheumatology clinics in England. We included men and women aged over 18 with disease durations over 12 months who met the 1987 criteria for classification of rheumatoid arthritis and NICE criteria for starting biologics in England. The NICE criteria comprise disease activity score for 28 joints >5.1 twice over one month apart after treatment with methotrexate and one other disease modifying drug.7 We excluded patients who unable or unwilling to give informed consent, had not had successful results with or had contraindications to all combinations of disease modifying drugs (including possible pregnancy), had contraindications to tumour necrosis factor inhibitors, had serious inter-current illness, or were taking high dose corticosteroids (>10 mg prednisolone).
administered as self completed questionnaires retrospectively for the previous three month period. Costs (for 2010–11 in £) were assessed from a health and social care perspective and were multiplied by two to represent the six month period before each assessment.

We assessed disease activity monthly by recording tender and swollen joint counts (28 joints), erythrocyte sedimentation rates, patients’ global assessments of disease activity (100 mm visual analogue scale), and the disease activity scores for 28 joints. Withdrawals from treatment or the trial were also recorded monthly together with details of drugs and adverse events.

An anonymised electronic data capture system collected clinical data except radiographs (www.medscinet.net).

Sample size calculation
Published data on 12 month changes in scores on the health assessment questionnaire in rheumatoid arthritis trials of tumour necrosis factor inhibitors (mean baseline score 1.7; reduction after treatment of 25%; standard deviation of change 0.4)\(^\text{10}\) and combination therapy with disease modifying drugs (mean baseline score 1.6; reduction after treatment of 31%; standard deviation of change 0.6)\(^\text{20}\) gave an average standard deviation for changes in health assessment questionnaire scores of 0.5.

The minimal clinically important change in scores on the health assessment questionnaire is 0.22,\(^\text{21}\) We based our sample size on testing the null hypothesis of a difference of >0.22 between the two treatments. With a (one-sided) testing level of 5%, we needed a sample size of 176 to achieve 90% power. We recruited 214 patients to allow for patients not receiving treatment or dropping out when treatment had started.

Randomisation
Potentially eligible patients were screened and reasons for non-entry recorded. Consenting patients were randomised in blocks of four with allocation stratified by region. MedSciNet generated the allocation sequence; trial staff had no prior knowledge of the allocation sequence. There were variable delays between randomisation and baseline assessments because patients received combination disease modifying drugs and tumour necrosis factor inhibitors through routine NHS systems.

Blinding
The trial was unblinded because it used treatment specific algorithms with the adjustment of multiple drug doses. Patients assessed their own disability and quality of life. Radiographs were read blinded.

Statistical methods
Baseline characteristics were summarised by randomisation group as means and standard deviations (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 basis. All participants had complete observations at baseline. Missing data at follow-up was imputed regardless of the reason(s) they was missing. For participants with missing outcomes, we used the baseline outcomes and other explanatory covariates (treatment group, sex, age, ethnicity, region, and disease duration) to impute the missing data, assuming unobserved measurements were missing at random (see appendix table A).

Linear regression evaluated 12 month outcomes. Univariate analyses were adjusted for region (design variable). Multivariable analyses were adjusted for sex, ethnicity, age, region, and duration of disease and baseline scores, which all influence disability. Generalised estimating equations with working correlations (auto-regressive with lag one) evaluated disease activity score for 28 joints and its components measured monthly. Treatment withdrawals and toxicities were compared with Fisher’s exact tests. These analyses compared treatment strategies ignoring subsequent treatment switches. In all analyses patients in the tumour necrosis factor inhibitor strategy were the reference group. Only the primary outcome was tested for non-inferiority. Other outcomes were compared for evidence of superiority of one or other treatment strategy.

Exploratory analyses examined good responders according to the European League Against Rheumatism (EULAR)\(^\text{22}\) with odds ratios and the development of remission based on disease activity scores for 28 joints\(^\text{23}\) with log rank tests on all observed data. No imputations were performed for these data. These analyses also examined differences between patients in the disease modifying drug strategy who stayed taking these drugs or switched to tumour necrosis factor inhibitors. Finally complete case analyses evaluated patients who followed the protocol and received 12 months’ treatment.

We also undertook a full economic evaluation, which will be reported separately.

Results
Patients and treatments
Participant flow and recruitment
Between September 2008 and December 2010, we screened 432 patients, randomised 214, and treated 205 (fig 1). Of these 205 treated patients, 147 (72%) completed 12 months of treatment; 16 (8%) were lost to follow-up; 42 (20%) discontinued the intervention and were followed-up; 16 (8%) stopped treatment because of toxicity (10 in combined drug strategy; six in tumour necrosis inhibitor factor strategy); five stopped (2%) because of disease progression (one and four, respectively); and 37 (18%) stopped for other reasons including patients’ decisions to stop treatment (21 and 16, respectively).

Baseline data and numbers analysed
Demographic and disease assessments were similar in both groups of treated patients (Table 1). All treated patients were analysed.
Fig 1 | Consort flowchart of study in patients with rheumatoid arthritis randomised to treatment with combinations of disease modifying drugs or tumour necrosis factor inhibitors

**Treatments**

Before randomisation all patients had received two disease modifying drugs (Table 1): 62 had received three; 77 were taking combinations of two or more disease modifying drugs; 24 were taking prednisone (mean dose 4 mg/day; range 1–7 mg). The treatments used are given in detail in appendix table B. In the disease modifying drug strategy the main initial combination was methotrexate and leflunomide (62 patients). Most patients received two or three disease modifying drugs; 10 received four or five drugs, though not concurrently. At six months, 46 patients were offered tumour necrosis factor inhibitors; 43 received them starting treatment at a mean of nine months. Steroids were given to 27 patients. Non-trial drugs were used by 88 patients in the first six months and by 90 in the second six months.

In the tumour necrosis factor inhibitor strategy the dominant initial biologic was adalimumab (58 patients). After six months, 16 patients received another tumour necrosis factor inhibitor. Steroids were given to 19 patients. Non-trial drugs were used by 94 patients in the first six months and by 91 in the second six months.

**Outcomes**

**Primary outcome**

Both groups had less disability, shown by falls in their scores on the health assessment questionnaire. Mean reductions were −0.30 (95% confidence interval −0.42 to −0.19) with the tumour necrosis factor strategy and −0.45 (−0.55 to −0.34) with the disease modifying drug strategy. Figure 2 shows that the difference between groups favoured the disease modifying drug strategy. The figure follows the recommendations of Piaggio and colleagues. It shows unadjusted regression coefficients with 95% confidence intervals. The non-inferiority margin is shown for the scores on the primary outcome health assessment questionnaire. The mean difference was −0.14 and the 95% confidence interval (−0.29 to 0.01) was below the prespecified non-inferiority boundary of 0.22. There were no pre-defined non-inferiority margins for the secondary outcome measures. Adjustment for baseline and demographic variables did not change this conclusion (appendix table C).

**Secondary outcomes**

Both groups had improved quality of life, shown by increases in EQ5D-3L utility scores and SF-36 summary scores, and some erosive progression, shown by increases in Larsen scores. Difference between groups favoured the disease modifying drug strategy with EQ5D-3L scores, SF-36 physical component summary scores, and Larsen scores and the tumour necrosis factor inhibitor strategy with SF-36 mental component summary scores (fig 2). With all four outcomes, 95% confidence intervals of the differences between groups included zero. Adjustment for baseline and demographic variables did not change these conclusions (appendix table D). Fifty eight patients withdrew from study treatments; there was no difference between strategies (32 in disease modifying drug strategy vs 26 in tumour necrosis factor strategy; Fisher’s exact test P = 0.44).

Baseline health and social care costs were similar in both groups. Compared with the tumour necrosis factor strategy, the disease modifying drug strategy reduced costs for months 0–6 by a mean of £3615 (95% confidence interval £4104 to £3182) and for months 6–12 by £1930 (£2599 to £1301).

Disease activity fell in both groups (fig 3). Initial falls were greater with the tumour necrosis factor inhibitor strategy, but with time the differences equalised. Over the whole 12 months the unadjusted difference between groups was 0.48 (95% confidence interval 0.17 to 0.79), favouring the tumour necrosis factor inhibitor strategy. The difference was predominantly because of changes in the erythrocyte sedimentation rate (appendix table E).

**Ancillary analyses**

**Switching treatments**

Patients in the disease modifying drug strategy who remaining taking disease modifying drugs (n=58) or switched to tumour necrosis factor inhibitors (n=46) had similar 12 month outcomes in all analyses. At six months the “switchers” had higher mean scores on the health assessment questionnaire (1.64 v 1.42) and disease activity scale for 28 joints (5.76 v 4.01).

**Exploratory analyses using all observed data**

Eighty patients had remissions (36 in disease modifying drug strategy, 44 in tumour necrosis factor inhibitor strategy) at any point in the trial. Only 30 patients (11 and 19, respectively) had sustained remissions. Time to first remission did not differ significantly between...
groups (log rank test P=0.09). More patients in the tumour necrosis factor inhibitor strategy, however, achieved early remission; after three months 16 patients were in remission compared with five in the disease modifying drug strategy.

Sixty six patients had good responses according to the European League Against Rheumatism at 12 months (37/94 in the tumour necrosis factor inhibitor strategy, 29/92 in the disease modifying drug strategy). The odds ratio of achieving a good response with the disease modifying strategy was 0.71 (95% confidence intervals 0.39 to 1.30) compared with the tumour necrosis factor inhibitor strategy.

Completer analysis
The results comparing treatments in the 147 complete cases (72 in disease modifying drug strategy, 75 in tumour necrosis factor inhibitor strategy) were similar to those seen in the intention to treat analysis (appendix table A).

Harms
Adverse events (Table 2) were common: 28 patients had serious adverse events (18 with the tumour necrosis factor inhibitor strategy; 10 with the disease modifying drug strategy; Fisher’s exact test P=0.11). One patient in the tumour necrosis factor strategy died from pneumonia and multiple organ failure. Sixteen patients (six and 10, respectively) stopped treatment because of toxicity (Fisher’s exact test P=0.44). Overall there were 1100 adverse events; more occurred with the disease modifying drug strategy (635 v 465). Infections that involved several body systems occurred in 54 patients in the tumour necrosis factor strategy and 30 patients in the disease modifying drug strategy.

Discussion

Interpretation
In patients with rheumatoid arthritis, our strategy of treatment with synthetic disease modifying drugs achieved non-inferior outcomes to the NICE approved strategy of treatment with tumour necrosis factor inhibitor over 12 months. It also cost substantially less. Our primary outcome—the score on the health assessment questionnaire—fell in both groups, indicating reduced disability at the trial endpoint. The difference between groups favoured the disease modifying drug strategy, with 95% confidence intervals

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**Table 1** Baseline demographic and clinical characteristics of patients with rheumatoid arthritis randomised to treatment with combinations of disease modifying drugs or tumour necrosis factor inhibitors. Figures are means (SD) unless stated otherwise.

<table>
<thead>
<tr>
<th>Demographic variables</th>
<th>Combination disease modifying drugs strategy (n=104)</th>
<th>Tumour necrosis factor inhibitor strategy (n=101)</th>
</tr>
</thead>
<tbody>
<tr>
<td>Age (years)</td>
<td>58 (13)</td>
<td>57 (11)</td>
</tr>
<tr>
<td>No (%) of women/men</td>
<td>73/31 (70/30)</td>
<td>79/22 (78/22)</td>
</tr>
<tr>
<td>No (%) by ethnic group:</td>
<td></td>
<td></td>
</tr>
<tr>
<td>White</td>
<td>89 (86)</td>
<td>92 (91)</td>
</tr>
<tr>
<td>Black (African, Caribbean, other)</td>
<td>6 (6)</td>
<td>2 (2)</td>
</tr>
<tr>
<td>Other</td>
<td>9 (9)</td>
<td>7 (7)</td>
</tr>
<tr>
<td>Median (IQR) duration of disease (years)</td>
<td>4.4 (1.6–9.9)</td>
<td>5.9 (2.2–13.4)</td>
</tr>
<tr>
<td>Height (m)</td>
<td>1.64 (0.11)</td>
<td>1.66 (0.09)</td>
</tr>
<tr>
<td>Weight (kg)</td>
<td>78 (20)</td>
<td>81 (17)</td>
</tr>
<tr>
<td>Median (IQR) BMI</td>
<td>29 (24–33)</td>
<td>29 (25–32)</td>
</tr>
</tbody>
</table>

**Clinical variables**

| Disease activity score for 28 joints | 6.2 (0.9) | 6.3 (0.8) |
| Tender joint count                | 16 (7)    | 18 (7)    |
| Swollen joint count               | 11 (6)    | 11 (7)    |
| ESR (mm in first hour)            | 33 (26)   | 30 (23)   |
| Patient global visual analogue score (mm) | 68 (20) | 68 (21) |
| Health assessment questionnaire score | 1.8 (0.6) | 1.9 (0.7) |
| Larsen score                      | 45 (42)   | 38 (39)   |
| EQ5D score                        | 0.39 (0.31) | 0.35 (0.31) |
| SF-36 physical component summary score | 28 (7) | 27 (7) |
| SF-36 mental component summary score | 43 (12) | 41 (12) |

**Previous disease modifying drug treatments (No of patients)**

| Methotrexate     | 98        | 97        |
| Sulfasalazine    | 68        | 56        |
| Leflunomide      | 27        | 29        |
| Other            | 48        | 49        |
| Three previous treatments | 33      | 29        |
| Combination drugs at screening | 38     | 39        |
| Prednisolone at screening (mean daily dose) | 16 (4 mg) | 8 (4 mg) |

BMI=body mass index; IQR=interquartile range; ESR=erythrocyte sedimentation rate.
12 months. Longer term observational and detailed results support using the combined drug strategy for patients who switched to tumour necrosis factor inhibitors.28

Both strategies improved quality of life similarly and resulted in minimal erosive progression. The tumour necrosis factor inhibitor strategy cost an additional average £5545 (€7570, $8586) per patient. Its main advantage was rapid falls in disease activity and more early remissions. As synthetic disease modifying drugs are “slow acting” agents,29 this difference is not surprising. Patients who did not respond to six months of treatment with disease modifying drugs and who switched to tumour necrosis factor inhibitors were not disadvantaged.

Over 12 months, health and social care costs were £5545 less in patients who were treated with the combined drug strategy. These reduced costs were associated with reduced scores on the health assessment questionnaire, which have immediate economic benefits.26 These reduced costs were associated with reduced scores on the health assessment questionnaire, which have immediate economic benefits.26

Economic modelling studies are needed to show whether this approach has any enduring benefits.26,29

Tumour necrosis factor inhibitors have many advantages. Their innovative nature, rapid effects, and ease of use attract patients and clinicians. Their defined mechanism of action contrasts with the uncertainties about the molecular effects of drugs like methotrexate. Combinations of lower cost synthetic disease modifying drugs, however, are relevant for advanced health economics and might be even more relevant in health economics where biologics are unaffordable.

### Generalisability

The patients in our trial had diverse ethnicities and deprivation levels and were seen in routine practice settings in geographically dispersed centres in England. We focused on patient centred outcomes, which are crucial for people with arthritis. Levels of disease activity replicated levels in national and international registers30,31 before and during treatment.

### Limitations

Our trial had several limitations. Firstly, many eligible patients did not participate, mainly because they did not consent. Although non-consenting patients could have responded differently to participants,32 participation levels replicated other English grant funded trials in rheumatoid arthritis30 and recent tumour necrosis factor inhibitors trials.33 Non-participation is likely to reflect patients’ concerns about all intensive treatments34 and our cautiously worded patient information sheet.35

Secondly, disease modifying drugs regimens varied because standardisation was impossible in this context. Thirdly, few trials in rheumatoid arthritis use the health assessment questionnaire as their primary outcome measure. It was relevant in our trial because it measures changes important to patients, is sensitive to improvements with all tested treatments,37 and helps NICE to determine treatment benefits. Scores on the health assessment questionnaire change less in those with late rheumatoid arthritis,38 but both groups had clinically important improvements, and the durations of disease in our patients were comparable with those in pivotal biologic trials.37,38 Although minimally important differences in scores might be less than 0.22 in routine practice,39 this lower difference would not change our conclusions.

Fourthly, our trial was un-blinded because blinding is impractical when many different treatments are used. The primary outcome, however, was self completed by patients and clinicians. Fifthly, our trial lasted only 12 months because when it was designed longer delays in assessing biologic treatments raised ethical concerns.

Finally, the effects of withdrawal and switching treatments need careful consideration. Only a few patients (16/205, 8%) were lost to follow-up and required the imputation of missing data. As the complete case analysis gave similar findings to the intention to treat analysis, it seems unlikely that withdrawals influenced our conclusions. Comparable numbers of patients withdrew from both trial arms, suggesting withdrawals were unlikely to be

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**Fig 3 | Changes in mean (SE) DAS28 scores (intention to treat analysis) in patients with rheumatoid arthritis randomised to treatment with combinations of disease modifying drugs or tumour necrosis factor inhibitors**

**Table 2 | Adverse events by body system in patients with rheumatoid arthritis randomised to treatment with combinations of disease modifying drugs or tumour necrosis factor inhibitors**

<table>
<thead>
<tr>
<th>Body system</th>
<th>Combination disease modifying drugs strategy (n=104)</th>
<th>Tumour necrosis factor inhibitor strategy (n=101)</th>
</tr>
</thead>
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<tr>
<td>Cardiovascular</td>
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<tr>
<td>Serious</td>
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<td>2</td>
</tr>
<tr>
<td>All</td>
<td>22</td>
<td>17</td>
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<tr>
<td>Digestive</td>
<td>0</td>
<td>148</td>
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<tr>
<td>Serious</td>
<td>4</td>
<td>60</td>
</tr>
<tr>
<td>All</td>
<td>1</td>
<td>76</td>
</tr>
<tr>
<td>Ear, nose, throat</td>
<td>0</td>
<td>88</td>
</tr>
<tr>
<td>Serious</td>
<td>1</td>
<td>7</td>
</tr>
<tr>
<td>All</td>
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<td>7</td>
</tr>
<tr>
<td>Endocrine/metabolic</td>
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<td>7</td>
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<tr>
<td>Serious</td>
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<td>7</td>
</tr>
<tr>
<td>All</td>
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<td>7</td>
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<tr>
<td>Genitourinary</td>
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<tr>
<td>Serious</td>
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<td>27</td>
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<tr>
<td>All</td>
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<td>27</td>
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<tr>
<td>Haematological</td>
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</tr>
<tr>
<td>Serious</td>
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<td>10</td>
</tr>
<tr>
<td>All</td>
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<td>10</td>
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<td>Mental</td>
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<td>All</td>
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<td>Musculoskeletal</td>
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<tr>
<td>All</td>
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<td>Nervous system</td>
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<td>Ophthalmological</td>
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<tr>
<td>Serious</td>
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<tr>
<td>Respiratory</td>
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<tr>
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<td>Skin</td>
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<tr>
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<td>47</td>
</tr>
<tr>
<td>All</td>
<td>2</td>
<td>47</td>
</tr>
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</table>

*As infections involved several different body systems, they could not be incorporated within table. In combination disease modifying drugs strategy, five serious adverse events involved an infection and 30 patients had infection. In tumour necrosis factor inhibitor strategy, seven serious adverse events involved an infection and 54 patients had infection.
influenced by the treatment strategies. Overall withdrawal rates were similar to those in comparable rheumatoid arthritis strategy trials involving biologics and disease modifying drugs.\textsuperscript{40–42} The frequencies with which patients discontinued tumour necrosis factor inhibitors were comparable with UK national registry data of routine practice results.\textsuperscript{43} The evidence suggests withdrawals in our trial were unlikely to have influenced our main conclusions.

**Overall evidence**

In early rheumatoid arthritis three head-to-head trials have shown that combinations of disease modifying drugs achieve similar benefits to tumour necrosis factor inhibitors.\textsuperscript{40–42} RACAT, the only other trial in established active rheumatoid arthritis,\textsuperscript{43} showed that triple therapy (methotrexate, sulfasalazine, and hydroxychloroquine) achieved similar benefits to etanercept plus methotrexate in incomplete methotrexate responders treated for 12 months. Our trial and RACAT had comparable results, despite differences in patients and trial design. They highlight the role of head-to-head trials against effective conventional comparators to evaluate expensive treatments.\textsuperscript{44}

Although toxicity remains a potential concern with combined disease modifying drugs because single trials like ours cannot fully assess risks, such combinations have been used for many years without evidence of major toxicity.\textsuperscript{45–47}

The current trial questions the status quo of use of biologics in patients with active rheumatoid arthritis in whom methotrexate does not achieve the required response. In these patients the clinical and economic evidence from our trial supports preferentially starting combinations of synthetic disease modifying drugs. We also believe that modernising biologic treatment regimens for rheumatoid arthritis requires more strategy trials. Increasing efficacy is important, and optimising cost effectiveness is crucial. Options include giving biologics to patients with rheumatoid arthritis who are likely to respond to specific agents,\textsuperscript{46,47} discontinuing biologics when patients do not fully respond, and tapering treatment when patients achieve sustained remissions.\textsuperscript{48}

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**Contributions**

DLS was chief investigator and grant holder and designed the study, developed the protocol, led the trial, searched literature, produced figures, interpreted data, and was responsible for writing paper and associated reports. FJ wrote the statistical analysis plan, undertook the main data analysis, produced tables for publication, and wrote the statistical section. VF was senior trial statistician and co-applicant on the grant, advised on the statistical analysis plan, reviewed all the data produced for the trial, and critically revised all statistical analyses. AGOU was additional trial statistician and independently imputed trial data for intention to treat analysis and checked all trial outcome analyses. DW was co-applicant on the grant and helped design study, was a major recruiter to the trial, and provided a critical review of the results and final paper. CK was a major recruiter to the trial and served on the trial steering committee and provided a critical review of the results and final paper. FB was a major recruiter to the trial and provided a critical review of the results and final paper. PM was independent chair of the trial steering committee and was responsible for oversight of the trial, provided substantial ongoing independent advice to the grant holders and funders, and provided a critical review of the results and the final paper. MH analysed all the economic data for the trial. AP was a grant-holder, devised the economic aspects of the trial, oversaw the economic analysis, wrote the economic report of the results and final paper. GHK was the chief statistician and grant-holder and supported the chief investigator in the design of the study, the ongoing conduct of the trial, data interpretation, and the content of the final paper and associated reports. DLS is guarantor.

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**Competing interests**

All authors have completed the ICMJE uniform disclosure form at www.icmje.org/coi_disclosure.pdf and declare: no support from any organisation for the submitted work; no financial relationships with any organisations that might have an interest in the submitted work in the previous three years; no other relationships or activities that could appear to have influenced the submitted work.

**Ethical approval**

This study was approved by University College London Hospital research ethics committee (MREC Ref 07/Q0505/57), and all patients gave written informed consent.

**Transparency declaration**

The lead author affirms that this manuscript is an honest, accurate, and transparent account of the study being reported; that no important aspects of the study have been omitted; and that any discrepancies from the study as planned (and, if relevant, registered) have been explained.

**Data sharing**

Anonymised patient level data and a technical and statistical appendix will be available from the corresponding author for inclusion in meta-analyses and other relevant similar academic endeavours.


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Appendix: Supplementary tables A-E