End of Clinical Trial Report

TICOPA: TIght COntrol of Psoriatic Arthritis: A randomised controlled trial to compare intensive management vs standard care in early psoriatic arthritis

1. Trial Summary

EudraCT	2007-004757-28
ISRCTN	ISRCTN30147736
Sponsor No.	RR07/8350
Sponsor	University of Leeds (Non-commercial sponsor), R&D Department, 34 Hyde Terrace, Leeds, LS2 9NL
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CTA Approval	08 APRIL 2008
Main REC Approval	01 FEBRUARY 2008
Current protocol version and date	Version 8.0; 24 November 2011
Full Title	TICOPA: TIght COntrol of Psoriatic Arthritis: A randomised controlled trial to compare intensive management vs standard care in early psoriatic arthritis
Phase of study	IV
Investigational Medicinal Products (IMPs)	Methotrexate: 15mg/wk for 4 weeks, 20mg/wk for 2 weeks, 25mg/wk for at least 6 weeks Sulphasalazine: 500mg od for 1 week, increasing by 500mg per week to 1g bd at week 4. Continue 1g bd for 4 weeks. Escalate to 40mg/kg/day maximum. Treatment is for at least 12 weeks. Cyclosporin: 1mg/kg/day for 4 weeks, 2mg/kg/day for 4 weeks, 3mg/kg/day for at least 4 weeks. Leflunomide: 10mg/day for 4 weeks, 20mg/day for at least 8 weeks. Etanercept: 50mg per week for at least 12 weeks. Infliximab: 5mg/kg per infusion. Infusions will be given for at least 12 weeks at week 0, 2, 6 and 8 weekly thereafter. Adalimumab: 40mg per fortnight for at least 12 weeks.
Treatment Groups	Patients will be randomised on a 1:1 basis to receive either intensive management or standard care.
Target number of patients	206
Final number patients recruited	206

Signed electronically by Dr Philip Helliwell on 03/05/2014

2. Trial Design

TICOPA is a multicentre, randomised, open-label, controlled, two-arm parallel group trial in patients with early psoriatic arthritis (PsA) designed to show whether intensive management of PsA improves clinical outcome compared to standard care.

Patients were randomised on a 1:1 basis to receive either intensive management (IM) or standard care (StdC). Randomisation was via minimisation and incorporated the minimisation factors centre and arthritis classification (oligo-arthritis vs. poly-arthritis).

The trial was powered for the pre-specified primary outcome, ACR20 response at 48 weeks post-randomisation. Based on previous data (1) a 50% response rate was assumed in the standard care arm at 48 weeks. A sample size of 93 evaluable patients per arm (total sample size 186) provided the trial with 80% power to detect a difference in ACR20 response rates of 20% between the two treatment arms at 48 weeks, based on a chi-squared test without continuity correction at the 2-sided 5% significant level. To account for 10% dropout, the target recruitment was 206 patients.

Study physicians and patients were aware of the allocated treatment arm. Follow-up assessments involving a full clinical assessment every 12 weeks were performed by a research nurse or metrologist masked to the allocated treatment arm.

Screening assessments took place within 28 days of the start of protocol treatment and all patients were required to be treated in the trial for a period of 48 weeks and followed up for safety up to 52 weeks.

Patients were recruited and randomised from eight UK secondary care rheumatology centres (Leeds Teaching Hospital Trust, Bradford Teaching Hospitals Trust, York District Hospital, Royal National Hospital for Rheumatic Diseases, Bath, Harrogate District Hospital, St Bartholomews Hospital London, North Tyneside General Hospital, Manchester Royal Infirmary). The first patient was randomised on 28/05/2008 and the last patient was randomised on 21/03/2012. The end of trial definition was defined as 30 days after the date of the last patient's last treatment visit at the 48 week time point. This corresponded to 10th May 2013.

3. Trial Objectives

The aim of the TICOPA trial was to establish whether, in treatment naïve early PsA patients, intensive management with evidence based therapies could improve clinical and imaging outcomes over 48 weeks. The principle hypothesis of this study is that tight control of inflammation in psoriatic arthritis using a treatment protocol and pre-defined objective targets for treatment will lead to an improvement in patients' disease activity and a reduction in radiological joint damage compared to standard care alone.

Primary objective:

To compare intensive management with standard care in terms of the proportion of patients achieving an ACR 20 (American Society of Rheumatology) response (2) at 48 weeks post-randomisation, in order to determine whether intensive management has superior clinical efficacy.

Secondary Objectives:

To compare intensive management with standard care in terms of:

- Additional clinical efficacy outcomes at 24 and 48 weeks, including:
  - ACR20 (24 weeks), ACR50 and ACR70
  - PASI 20, PASI 75 and PASI 90
  - Change in Sharp-van der Heijde Score

- ASAS 20 and ASAS 40
- Change in enthesitis score
- Change in dactylitis score
- Change in mNAPSI
- Change in HAQ
- Change in other scores (including BASDAI, tender and swollen joint counts, patient and clinician VAS scores)
- MDA score

- Comparison of Quality of Life (QoL), using PsAQoL between intensive management and standard care at baseline, 24 and 48 weeks

- Assessment of cost effectiveness at 12, 24 and 48 weeks

- Comparison of safety outcomes over the course of the treatment until 52 weeks

- Comparison of imaging efficacy outcomes including change in Psoriatic Arthritis Magnetic Resonance Imaging Score (PsAMRIS) and ultrasound assessment of disease at 48 weeks in order to assess inflammation and damage.

4. Population

Patients with the following characteristics were eligible for the study:

1. Patients with a diagnosis of psoriatic arthritis by a consultant Rheumatologist with less than 24 months disease duration.
2. Active disease defined by at least one tender or swollen joint or active enthesitis.
3. Age ≥18 years at the time of signing the informed consent form and either male or female patients.
4. Patient understands the objectives of the study and is able and willing to sign the Informed Consent Form.
5. Women of child bearing potential (WCBP) and men whose partners are WCBP must use at least one adequate birth control measure whilst receiving protocol treatment and should continue such precautions after receiving the last dose of protocol treatment as indicated in the relevant SmPC.
6. Adequate full blood count within 28 days before randomisation:
    a. Haemoglobin count > 8.5 g/dL
    b. White blood count (WBC) > 3.5 x 10^9/L
    c. Absolute neutrophil count (ANC) > 1.5 x 10^9/L
    d. Platelet count > 100 x 10^9/L
7. Adequate hepatobiliary function within 28 days before randomisation:
    a. ALT and/or AST levels must be within 3 times the upper limit of normal range (ULN) for the laboratory conducting the test.
8. The patient must be able to adhere to the study visit schedule and other protocol requirements.

Patients were excluded from this study for any of the following reasons:
1. Previous treatment for articular disease with disease modifying drugs (DMARDs) including, but not limited to, methotrexate, sulfasalazine, leflunomide.
2. Women who are pregnant, lactating or planning pregnancy within 6 months of their last dose of protocol treatment.
3. Use of any investigational agents within 4 weeks or within 5 half-lives of the investigational agent, whichever is longer, prior to randomisation.

5. Treatment

Patients received either intensive management or standard care for a period of 48 weeks, with follow-up of safety up to 52 weeks. Patients randomised to the intensive management arm were seen every 4 weeks by the study physician and treated according to a strict treatment protocol (Appendix 1). At each visit, the minimal disease activity (MDA) criteria were assessed. These criteria include assessment of the following: (i) a full 68 tender and 66 swollen joint count, (ii) Psoriasis Area Severity Index (PASI), (iii) enthesitis count, (iv) patient global disease activity (VAS), (v) patient pain (VAS), and (vi) the Health Assessment Questionnaire (HAQ). Treatment with DMARDs was escalated to the maximum dose according to the protocol in Appendix 1 if patients did not achieve the MDA criteria (see Appendix 2 for the full criteria of response). In the case of drug intolerance, that drug was discontinued and the next step in the protocol was initiated. Any patient who could not tolerate the maximum dose specified in the protocol due to toxicity or intolerance, was permitted to continue on the highest tolerable dose and then progress to the next step in the protocol if required. Patients achieving these criteria continued on their current therapy. Intra-articular and intra-muscular steroids were also used in disease control. Patients were offered local joint injections to active joints and/or intramuscular steroid by the physicians if considered appropriate.

Patients randomised to the standard care arm were treated in a general rheumatology outpatient clinic supervised by a consultant rheumatologist and including trainee rheumatologists working under supervision. These patients were reviewed every 12 weeks or more often if clinically indicated, with no formal measures of disease activity used in clinical decision making. There was no requirement or restriction on prescribing within this arm of the study.

Radiographs of the hands and feet were performed at baseline and 48 weeks. They were scored using the modified van der Heijde-Sharp scoring method for PsA for both erosion and joint space narrowing. Scoring was done by two trained rheumatologists (PSH and LCC) by consensus. All films were scored paired but blinded to treatment arm and sequence.

6. Participant Flow

See Appendix 3 for the trial CONSORT diagram.

A total of 344 patients were considered for entry into the trial. A total of 138 patients (40.1%) screened did not go on to be randomised: 82 (59.4%) were clinically ineligible, 44 (31.9%) declined participation and 12 (8.7%) were excluded for other reasons.

A total of 206 patients have been randomised, 101 (49.0%) were randomised into the intensive management arm and 105 (51.0%) were randomised into the standard care arm.

In the intensive management arm, 90 patients (89.1%) completed follow-up to week 48 with a similar proportion in the standard care arm (92 (87.6%)). No patients were found to be ineligible for the trial post-randomisation. Four patients in the intensive management arm withdrew from follow-up and/or treatment, with a further one patient withdrawn by the clinician, compared to seven patients in the standard care arm. A further eleven patients were lost to follow-up, with a similar number in both treatment arms (6 (5.9%) IM, 5 (4.8%) StdC).

The intention-to-treat (ITT) population comprises of all 206 patients. The evaluable patient population (i.e. the population of patients for which the primary endpoint could be derived) consists of 89 intensive management patients and 83 standard care patients.

7. Criteria for Evaluation

The primary endpoint was:

- Proportion of patients achieving an ACR 20 response at 48 weeks post-randomisation.

The ACR20 is a composite response measure developed for rheumatoid arthritis (RA) and requires an improvement of at least 20% in both the tender and swollen joint counts and a 20% improvement in three out of five criteria from baseline to 48 weeks: (i) patient global assessment of disease activity (VAS); (ii) physician global assessment of disease activity (VAS); (iii) patient assessment of pain (VAS); (iv) Health Assessment Questionnaire (HAQ), and (v) an inflammatory marker (Erythrocyte Sedimentation Rate (ESR) or C-reactive Protein (CRP)). This has now been validated as a discriminative outcome measure in PsA (2).

The key secondary endpoints were:

- ACR 50 and 70 at 48 weeks post-randomisation
- PASI 75 at 48 weeks post-randomisation
- X-ray Van der Heijde score at 48 weeks post-randomisation
- Cost effectiveness ratio using quality adjusted life year (QALY) outcome measures at 12, 24 and 48 weeks

The additional secondary endpoints to be summarised at 12, 24, 36 and 48 weeks were:

- ACR 20, ACR 50 and ACR 70 (baseline, 12, 24 and 36 weeks only)
- PASI 75 (baseline, 12, 24 and 36 weeks only)
- PASI 20 and PASI 90
- ASAS 20 and ASAS 40
- mNAPSI score
- Enthesitis score
- Dactylitis score
- PsAQoL
- HAQ
- BASDAI 50
- Total tender joint count
- Total swollen joint count
- Patient and clinician VAS scores
- MDA
- MRI and US scores (baseline and 48 weeks only)
- Safety and toxicity

8. Statistical Methods

The cut-off date for the data for analysis was 09/08/2013. All data entered onto the database at this time were included in the analysis. The statistical analysis plan was the responsibility of the CTRU Statistician and was written and signed off as the final version prior to the final data download and statistical analysis for the trial.

The analysis of primacy for the primary endpoint was based on the intention-to-treat (ITT) population. A multiple imputation approach was used to impute missing ACR component data at baseline, 12, 24, 36 and 48 weeks post-randomisation.

Each of the imputed datasets were analysed separately using a multivariate logistic regression model to assess the effect of treatment on the odds of patients achieving ACR20 at 48 weeks post-randomisation, adjusting for arthritis classification (oligoarticular vs polyarticular) and randomising centre. Centres recruiting 12 or less patients were combined in order to prevent model convergence problems. Results were combined using Rubin's rules (3). In addition, a univariate analysis was performed on those patients with an evaluable ACR20 response at 48 weeks (evaluable patient population). The difference in the proportion of patients achieving an ACR20 response between the treatment arms was compared using a chi-squared test without continuity correction.

Multiple logistic regression analysis adjusting for the minimisation factors (arthritis classification and

randomising centre) was used to compare the key secondary outcomes, ACR50/70 (ITT population) and PASI75 (evaluable patient population for the PASI75) at 48 weeks post-randomisation.

The difference in the median change in modified X-ray van der Heidje-Sharp (vdH-S) score (baseline – week 48) was compared between the treatment arms using the Wilcoxon Rank-Sum test.

Cost-effectiveness was assessed using within trial incremental cost effectiveness ratios, comparing the costs and benefits of a tight control approach to that of standard care over the trial duration.

Additional secondary outcomes were summarised by treatment arm and assessment time point.

All statistical analyses were carried out in SAS version 9.2. Multiple imputation of the missing ACR20 component data was performed in Stata version 12.0. All statistical testing was performed at the 2-sided 5% significance level.

9. Results

9.1 Enrolment

Two hundred and six patients were randomised between May 2008 and March 2012 (Appendix 4): 115 patients (55.8%) at Chapel Allerton Hospital, Leeds; 43 (20.9%) at St Luke's Hospital, Bradford; 18 (8.7%) at York District Hospital, York; 6 (2.9%) at St Bartholomew's Hospital, London; 12 (5.8%) at Royal National Hospital For Rheumatic Disease, Bath; 5 (2.4%) at North Tyneside Hospital, Newcastle; 5 (2.4%) at Harrogate District Hospital, Harrogate; 2 (1.0%) at Manchester Royal Infirmary, Manchester.

9.2 Treatment

Of the 206 patients randomised 101 were allocated to intensive management and 105 were allocated to standard management.

Methotrexate (MTX) monotherapy was used in 26·7% (n=27) of intensive management patients throughout the duration of the trial compared to 60·0% (n=63) in the standard care arm. A higher proportion of intensive management patients were treated with combination DMARDs (73·3% (n=74) IM, 28·6% (n=30) StdC) and biologic therapies (MTX + biologic: 38·6% (n=39) IM, 6·7% (n=7) StdC) during the course of the trial compared to standard care. All patients in the intensive management arm (n=101) reached an MTX dose level of at least 15mg/week by their 12 week visit compared to 66·7% (n=70) of standard care patients. A higher proportion of intensive management patients reached an MTX dose level of at least 20 mg/week (90·1% (n=91) TC vs. 29·5% (n=31) StdC) and of at least 25mg/wk (82·2% (n=83) TC, 7·6% (n=8) StdC) by their 12 week assessment compared to the standard care arm. Over the duration of the trial, patients in the intensive management arm received more steroid treatment in the form of intra-articular or intra-muscular injections compared to those in the standard care arm (median (IQR): 120mg (0, 260) per patient over 48 weeks (TC), 80mg (0, 160) (StdC)) but doses overall were relatively low.

9.3 Effectiveness

Primary endpoint

At 48 weeks, in the ITT population there was significant evidence that the odds of achieving ACR20 response at 48 weeks were greater in the intensive management arm than in the standard care arm after adjusting for centre and arthritis classification (odds ratio (OR) 1·91, 95% CI 1·03, 3·55, p=0·0392). In the evaluable patient population, 55 (61·8%) of 89 patients in the intensive management arm showed ACR20 response at 48 weeks compared with 37 (44·6%) of 83 patients receiving standard care. There was significant evidence of a difference in the proportion of patients achieving ACR20 response (IM – StdC: 17·2% (95% CI 2·5%, 31·9%), p=0·0237).

Key secondary endpoints

In the ITT population, there was significant evidence that the odds of achieving ACR50 (OR: 2·36, 95% CI: 1·25, 4·47, p=0·0081) and ACR70 (OR: 2·64, 95% CI: 1·32, 5·26, p=0·0058) at 48 weeks were greater in the intensive management arm compared to the standard care arm. In the evaluable patient population, the odds of achieving PASI75 response at 48 weeks were also significantly greater in the intensive management arm (PASI75 OR: 2·92, 95% CI: 1·51, 5·65, p=0·0015).

Radiographs were available for 195 (94·7%) patients at baseline and 176 (85·4%) at follow up. At baseline, the mvdH-S scores were low with a median score of 8·0 (IQR: 2·0, 16·0) predominantly due to joint space narrowing. There was no evidence of a difference in the change in mvdH-S score between the treatment arms (p=0·9779) as the median change in both arms was zero. Although median erosion scores were zero, of the 195 patients with available radiographs, 25·1% of patients had some erosive disease at baseline rising to 30·7% at 48 weeks. IQR scores for erosions were greater for the feet than the hands, although overall IQR scores were low for these patients.

9.4 Toxicity and Serious Adverse Events

Serious adverse events (SAEs) were reported in 20 (9·7%) of 206 patients and were more common in the intensive management arm with 25 SAEs observed in 14 patients (13·9%) compared to eight SAEs observed in six patients (5·7%) in the standard care arm. In patients experiencing an event, a similar median number of SAEs were reported between the treatment arms (1·0 (1·0, 6·0) IM, 1·0 (1·0, 2·0) StdC). Ten SAEs were suspected to be related to drug therapy, with eight in the intensive management arm (cellulitis (n=2), pneumonia (n=1), chest infection (n=1), MSK chest pain (n=1), raised LFTs (n=1), collapse and pancytopenia (n=1), anaphylaxis (n=1)) and two in the standard care arm (migraine, septic arthritis). There were no unexpected serious adverse events or deaths.

Adverse events (AEs) were reported in 179 (86·9%) of 206 patients and were more common in patients in the intensive management arm compared to the standard care arm (97·0% (n=98) IM, 77·1% (n=81) StdC). In patients experiencing an event, a higher median number of AEs were reported in the intensive management arm (6·0 (range: 1·0, 20·0)) compared to the standard care arm (3·0 (range: 1·0, 10·0)). Of all the AEs reported (n=866), the most commonly reported AEs were nausea (10·6% of AEs), liver abnormalities (8·8% of AEs), and infections (common cold) (6·9% of AEs).

A similar proportion of AEs were suspected to be related to drug therapy in both arms (68·2% IM, 72·8% StdC).

10. Conclusions

This study is the first to show that a treat to target approach can improve clinical outcomes for patients with early PsA, specifically the ACR20 over a period of 48 weeks. Treat to target using a “tight control” (intensive management) strategy improved both articular and skin outcomes with the greatest benefits seen with more stringent outcome measures such as ACR70. There was no difference seen in radiographic progression between the two arms. Adverse events were seen reported more often in the intensive managment arm.

11. Publications

1. Coates LC, Navarro-Coy N, Brown SR, Brown S, McParland L, Collier H, Skinner E, Law J, Moverley AR, Pavitt S, Hulme C, Emery P, Conaghan PG, Helliwell PS. The TICOPA protocol (TIght COntrol of Psoriatic Arthritis): a randomised controlled trial to compare intensive management versus standard care in early psoriatic arthritis. *BMC Musculoskeletal Disorders* 2013 March **14**:101

12. Presentations made

1. Coates LC, Moverley AR, McParland L, Brown S, Collier H, Law J, Brown SR, Corrigan N, Navarro-Coy N, Emery P, Conaghan PG, Helliwell PS. Results of a randomised controlled trial comparing tight control of early psoriatic arthritis (TICOPA) with standard care: tight control improves outcome. Presented at the American College of Rheumatology Annual Meeting 2013, San Diego, USA.

2. Coates LC, Moverley AR, McParland L, Brown S, Collier H, Brown SR, Navarro-Coy N, Emery P, Conaghan PG, Helliwell PS. Effect of tight control of inflammation in early psoriatic arthritis (TICOPA): a multicentre, open-label, randomised, controlled trial: Academy of Medical Sciences Spring Meeting 2014 on 26th February 2014

13. References

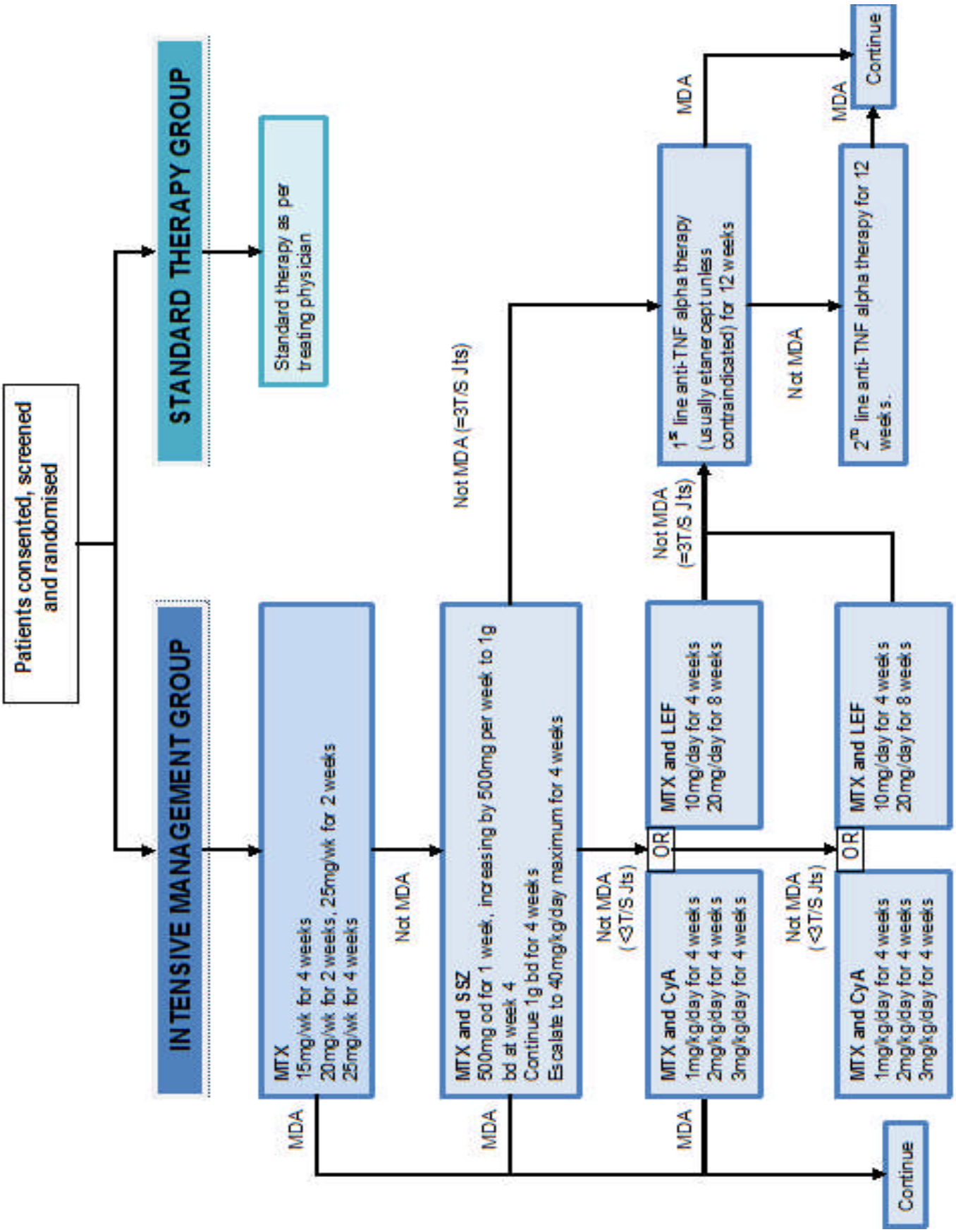
1. Healy PJ, Helliwell PS. Measuring dactylitis in clinical trials: which is the best instrument to use? J Rheumatol 2007;34(6):1302-6.

2. Feslon DT, Anderson JJ, Boers M, Bombardier C, Furst D, Goldsmith C *et al*. American College of Rheumatology preliminary core set of disease activity measures for rheumatoid arthritis clinical trials. *Arthritis Rheum* 1993;36:729-40.

3. Rubin DB. Inference and missing data. *Biometrika* 1976;63:581-90.

Appendices

Appendix 1. Study Flow Diagram



Appendix 2. Criteria of Response

Patients in the intensive management - "tight control" arm was assessed every 4 weeks to determine whether they have reached "Minimal Disease Activity". Minimal disease activity or MDA is defined as any patient who meets at least 5 of the 7 following criteria:

- Tender joint count ≤1
- Swollen joint count ≤1
- PASI ≤1
- Patient pain VAS ≤15
- Patient global disease activity VAS ≤20
- HAQ ≤0.5
- Enthesitis count ≤1

Patients who achieved these criteria continued on their current therapy. If patients did not achieve these criteria, therapy was escalated according to the flow diagram in Section 4, unless there was a specific reason for not escalating treatment.

A partial response is classed as an improvement in the number cut points achieved from the previous visit or an improvement in the patient's condition in the treating physician's opinion. Those obtaining MDA (5 or more cut points) cannot be considered partial responders by definition.

Patients in the standard care group had their response assessed by their physician at their clinical visits separately to their independent response assessment as part of the study. No standard response criteria are required to be used for the physician's assessment as per usual practice.

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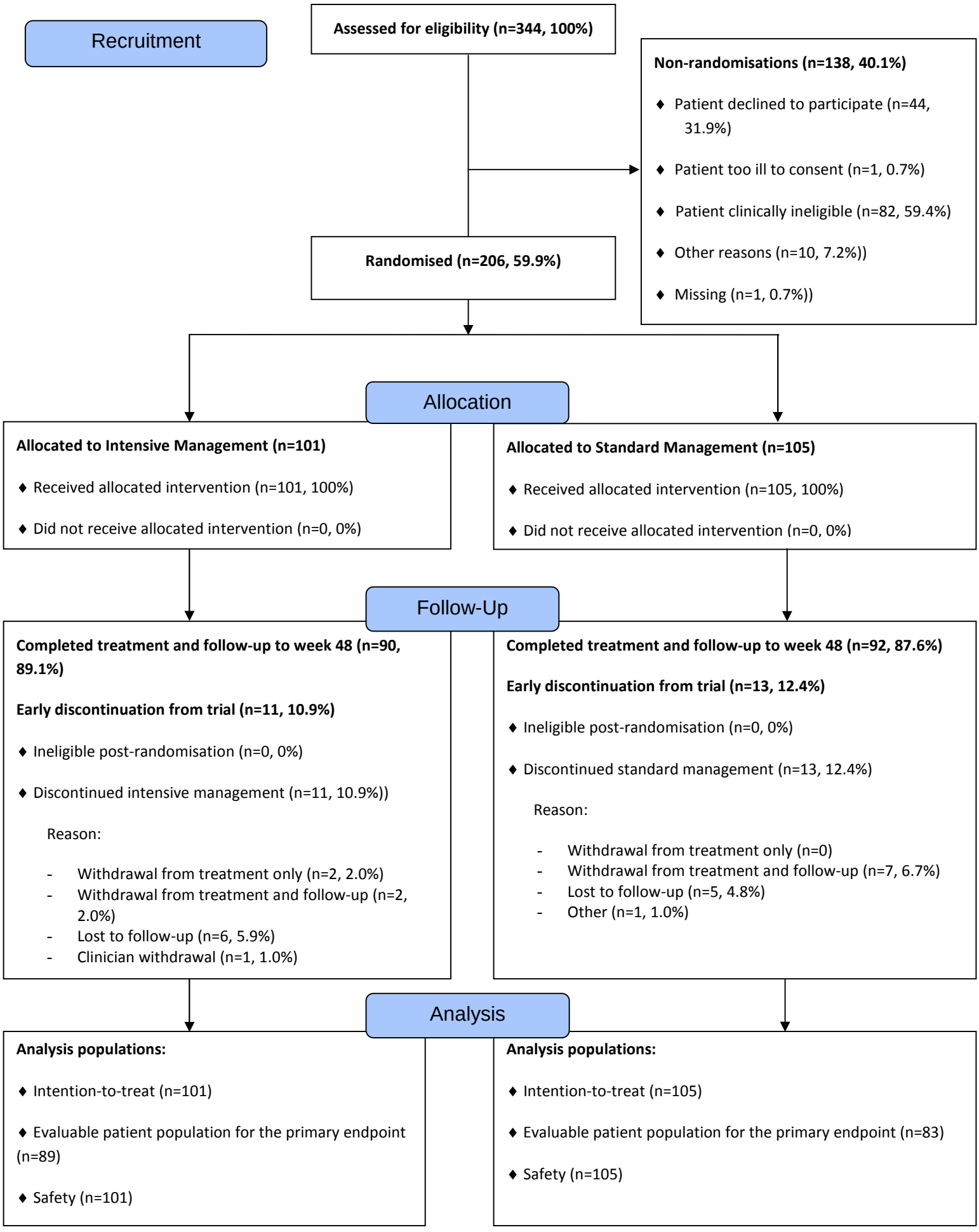
Appendix 3. CONSORT Diagram



Appendix 4. Recruitment Chart