Clinical trial results:
A randomised controlled single-blind trial to compare intensive management vs standard care in early psoriatic arthritis

Summary

EudraCT number	2007-004757-28
Trial protocol	GB
Global end of trial date	10 May 2013

Results information

Result version number	v1 (current)
This version publication date	19 March 2016
First version publication date	19 March 2016
Summary attachment (see zip file)	End of Trial reported submitted to MHRA (TICOPA_End of Trial Report_v1 0.pdf)

Trial information

Trial identification

Sponsor protocol code	RR07/8350

Additional study identifiers

ISRCTN number	ISRCTN30147736
ClinicalTrials.gov id (NCT number)	-
WHO universal trial number (UTN)	-

Notes:

Sponsors

Sponsor organisation name	University of Leeds
Sponsor organisation address	R&D Office, 34 Hyde Terrace, Leeds, United Kingdom, LS2 9LN
Public contact	Regulatory and Governance Affairs Manager, CTRU, University of Leeds, Leeds, LS2 9JT, medctruq@leeds.ac.uk
Scientific contact	Regulatory and Governance Affairs Manager, CTRU, University of Leeds, Leeds, LS2 9JT, medctruq@leeds.ac.uk

Notes:

Paediatric regulatory details

Is trial part of an agreed paediatric investigation plan (PIP)	No
Does article 45 of REGULATION (EC) No 1901/2006 apply to this trial?	No
Does article 46 of REGULATION (EC) No 1901/2006 apply to this trial?	No

Notes:

Results analysis stage

Analysis stage	Final
Date of interim/final analysis	09 August 2013
Is this the analysis of the primary completion data?	Yes
Primary completion date	10 May 2013
Global end of trial reached?	Yes
Global end of trial date	10 May 2013
Was the trial ended prematurely?	No

Notes:

General information about the trial

Main objective of the trial:

To compare intensive management with standard care in terms of the proportion of patients achieving an ACR20 response at 48 weeks post-randomisation, in order to determine whether intensive management has superior clinical efficacy.

Protection of trial subjects:

Inclusion/Exclusion: Eligibility criteria were designed with patient safety as a primary concern and therefore no one is unfairly excluded from or included in the trial. Consent: Patients were provided with written information about the trial and verbal information from a member of the local research team. Informed consent was taken by an authorised clinically and GCP trained member of staff who will ensure that the person understands the purpose and nature of the study and what it involves, the benefits, risks and burdens and the alternative treatments available. They will also ensure the patient is able to retain the information long enough to make an effective decision with free choice. All information collected during the course of the trial will be kept strictly confidential. Information will be held securely on paper and electronically at the Clinical Trials Research Unit (CTRU). The CTRUcomply with all aspects of the 1998 Data Protection Act.

Background therapy: -

Evidence for comparator: -

Actual start date of recruitment	28 May 2008
Long term follow-up planned	No
Independent data monitoring committee (IDMC) involvement?	Yes

Notes:

Population of trial subjects

Subjects enrolled per country

Country: Number of subjects enrolled	United Kingdom: 206
Worldwide total number of subjects	206
EEA total number of subjects	206

Notes:

Subjects enrolled per age group

In utero	0
Preterm newborn - gestational age < 37 wk	0
Newborns (0-27 days)	0
Infants and toddlers (28 days-23 months)	0
Children (2-11 years)	0

Adolescents (12-17 years)	0
Adults (18-64 years)	196
From 65 to 84 years	10
85 years and over	0

Subject disposition

Recruitment

Recruitment details:

Patients were recruited and randomised from eight UK secondary care rheumatology centres. The first patient was randomised on 28/05/2008 and the last patient was randomised on 21/03/2012.

Pre-assignment

Screening details:

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 (59.9%) screened, went on to be randomised into the trial.

Pre-assignment period milestones

Number of subjects started	206
Number of subjects completed	206

Period 1

Period 1 title	Main Trial (overall period)
Is this the baseline period?	Yes
Allocation method	Randomised - controlled
Blinding used	Single blind
Roles blinded	Assessor[1]

Blinding implementation details:

The follow-up assessments were performed by a research nurse or metrologist blinded to the allocated treatment group.

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 by consensus. All films were scored paired but blinded to treatment arm and sequence.

Arms

Are arms mutually exclusive?	Yes
Arm title	Intensive Management

Arm description:

First Line Therapy: Methotrexate (12 weeks minimum treatment before next line treatment can start, unless not tolerated). Second Line Therapy: Methotrexate plus Sulfasalazine (12 weeks minimum treatment before next line treatment can start, unless not tolerated). Third Line Therapy Methotrexate plus Leflunomide OR Cyclosporin OR Anti TNF therapy (Etanercept, Infliximab OR Adalimumab) (12 weeks minimum treatment before alternative third line therapy can start). Decision for order of third line therapy was that of the clinician based on clinical contraindications and NICE Guidance.

Arm type	Experimental
Investigational medicinal product name	Methotrexate
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

First Line Treatment. Oral methotrexate and oral folic acid; for contraindications to oral methotrexate, or if parenteral therapy was thought more appropriate, patients were prescribed parenteral methotrexate using the same dosing regime as for oral therapy. Methotrexate commenced at 15mg once a week with oral folic acid 5mg daily, except the day methotrexate was taken, for the first four weeks. The methotrexate dose was increased to 20mg per week from week 4 for an additional 2 weeks and then

increase to 25mg weekly for the remaining 6 weeks until the 12 week assessment. Providing that the drug was tolerated by the patient a trial of a minimum of 12 weeks therapy was given before changing or adding an alternative DMARD. In the event of minor side effects, then the highest tolerable dose was maintained. In the case of major problems with intolerance or toxicity, this therapy was stopped and the next step in the protocol started

Investigational medicinal product name	Sulfasalazine
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Second Line Treatment = Sulfasalazine + Methotrexate. Standard escalating dose of Sulfasalazine over the first four weeks, commencing at 500mg per day and increasing weekly to achieve a standard dose of 1g bd at the end of this period (500mg od for one week, 500mg bd for one week, 1g morning and 500mg in the evening for one week, 1g bd thereafter). Maintain the dose of 1g bd for a further 4 weeks. In the case of partial response after 8 weeks of therapy, titrate the dose up to a maximum of 40mg/kg/day in divided doses if tolerated. Providing that the drug was tolerated by the patient a trial of a minimum of 12 weeks therapy was given before changing or adding an alternative DMARD. In the event of minor side effects, if a patient was unable to tolerate the dose of the drug defined in the protocol due to toxicity or intolerance, then the highest tolerable dose was maintained. In the case of major problems with intolerance or toxicity, stop and move to next step in protocol

Investigational medicinal product name	Leflunomide
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Tablet
Routes of administration	Oral use

Dosage and administration details:

Leflunomide in addition to Methotrexate = Third Line Treatment. Leflunomide or Cyclosporin could be chosen. The choice between leflunomide and cyclosporin was be made by the treating physician based on their assessment of the individual patient and that patient's co-morbidities (if any) and NICE criteria. Leflunomide was started at a dose of 10mg daily, increasing to 20mg daily after 4 weeks if tolerated. Providing that the drug was tolerated by the patient a trial of a minimum of 12 weeks therapy was given before changing or adding an alternative DMARD. In the event of minor side effects, if a patient was unable to tolerate the dose of the drug defined in the protocol due to toxicity or intolerance, then the highest tolerable dose was maintained. In the case of major problems with intolerance or toxicity, this therapy was stopped and the next step in the protocol started.

Investigational medicinal product name	Cyclosporin
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Capsule, soft
Routes of administration	Oral use

Dosage and administration details:

Cyclosporin in addition to Methotrexate = Third Line Treatment. Leflunomide or Cyclosporin could be chosen. The choice between leflunomide and cyclosporin was be made by the treating physician based on their assessment of the individual patient and that patient's co-morbidities (if any) and NICE criteria. Cyclosporin commenced at 1mg/kg daily in divided doses for the first four weeks. The dose was then escalated to 2mg/kg/day for the second 4 week period and then 3mg/kg/day thereafter. Providing that the drug was tolerated by the patient a trial of a minimum of 12 weeks therapy was given before changing or adding an alternative DMARD. In the event of minor side effects, if a patient was unable to tolerate the dose of the drug defined in the protocol due to toxicity or intolerance, then the highest tolerable dose was maintained. In the case of major problems with intolerance or toxicity, this therapy was stopped and the next step in the protocol started.

Investigational medicinal product name	Etanercept
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Third line therapy if the NICE Criteria and BSR Guidelines were met. Etanercept was given at a dose of 50mg per week by subcutaneous injection. Providing that the drug was tolerated by the patient a trial

of a minimum of 12 weeks therapy was given before changing or adding an alternative DMARD. If the patient does not meet the MDA criteria for PsA after 12 weeks of therapy with a TNF blocker, an alternative anti-TNF therapy was commenced for a 12 week period. Where possible, a second-line anti-TNF therapy was chosen to have an alternative mode of action to the first TNF therapy. In the case of major problems with intolerance or toxicity during the 12 week trial, therapy was stopped and an alternative anti-TNF therapy started.

Investigational medicinal product name	Infliximab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Powder for solution for injection/infusion
Routes of administration	Intravenous use

Dosage and administration details:

Third line therapy if the NICE Criteria and BSR Guidelines were met.Infliximab was given at a dose of 5mg/kg per infusion at week 0, 2, 6 and 8 weekly thereafter. Providing that the drug was tolerated by the patient a trial of a minimum of 12 weeks therapy was given before changing or adding an alternative DMARD. If the patient does not meet the MDA criteria for PsA after 12 weeks of therapy with a TNF blocker, an alternative anti-TNF therapy was commenced for a 12 week period. Where possible, a second-line anti-TNF therapy was chosen to have an alternative mode of action to the first TNF therapy. In the case of major problems with intolerance or toxicity during the 12 week trial, therapy was stopped and an alternative anti-TNF therapy started.

Investigational medicinal product name	Adalimumab
Investigational medicinal product code	
Other name	
Pharmaceutical forms	Solution for injection
Routes of administration	Subcutaneous use

Dosage and administration details:

Third line therapy if the NICE Criteria and BSR Guidelines were met. Adalimumab was given at a dose of 40mg per fortnight by subcutaneous injection. Providing that the drug was tolerated by the patient a trial of a minimum of 12 weeks therapy was given before changing or adding an alternative DMARD. If the patient does not meet the MDA criteria for PsA after 12 weeks of therapy with a TNF blocker, an alternative anti-TNF therapy was commenced for a 12 week period. Where possible, a second-line anti-TNF therapy was chosen to have an alternative mode of action to the first TNF therapy. In the case of major problems with intolerance or toxicity during the 12 week trial, therapy was stopped and an alternative anti-TNF therapy started.

Arm title	Standard Therapy

Arm description:

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.

Arm type	No intervention

No investigational medicinal product assigned in this arm

Notes:

[1] - The roles blinded appear inconsistent with a simple blinded trial.

Justification: Follow up assessments involved a full clinical assessment at 12 weekly intervals to 48 weeks; entailing a physical examination, a full clinical disease assessment, concomitant medical history, and obtainment of safety and efficacy bloods. The follow-up assessment were performed by a research nurse or metrologist blinded to the allocated treatment group.

Number of subjects in period 1	Intensive Management	Standard Therapy
Started	101	105
Completed Treatment and Follow up	90	92
Completed	90	92
Not completed	11	13
Physician decision	1	-

Patient withdrawal from treatment and follow up	2	7
Lost to follow-up	6	6
Patient withdrawal from treatment	2	-

Baseline characteristics

Reporting groups	
Reporting group title	Intensive Management
Reporting group description:	
First Line Therapy: Methotrexate (12 weeks minimum treatment before next line treatment can start, unless not tolerated). Second Line Therapy: Methotrexate plus Sulfasalazine (12 weeks minimum treatment before next line treatment can start, unless not tolerated). Third Line Therapy Methotrexate plus Leflunomide OR Cyclosporin OR Anti TNF therapy (Etanercept, Infliximab OR Adalimumab) (12 weeks minimum treatment before alternative third line therapy can start). Decision for order of third line therapy was that of the clinician based on clinical contraindications and NICE Guidance.	
Reporting group title	Standard Therapy
Reporting group description:	
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.	

Reporting group values	Intensive Management	Standard Therapy	Total
Number of subjects	101	105	206
Age categorical Units: Subjects			
In utero			0
Preterm newborn infants (gestational age < 37 wks)			0
Newborns (0-27 days)			0
Infants and toddlers (28 days-23 months)			0
Children (2-11 years)			0
Adolescents (12-17 years)			0
Adults (18-64 years)			0
From 65-84 years			0
85 years and over			0
Age continuous Units: years			
median	46	45	
full range (min-max)	18 to 81	19 to 71	-
Gender categorical Units: Subjects			
Female	48	50	98
Male	53	55	108
Arthritis classification Units: Subjects			
Poly-articular	74	75	149
Oligo-articular	27	30	57

Subject analysis sets	
Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population is defined all randomised patients, regardless of if they are ineligible, withdraw, don't comply with the protocol, are lost to follow-up or don't receive any study treatment.

Reporting group values	Intention-to-treat		
Number of subjects	206		
Age categorical Units: Subjects			
In utero Preterm newborn infants (gestational age < 37 wks) Newborns (0-27 days) Infants and toddlers (28 days-23 months) Children (2-11 years) Adolescents (12-17 years) Adults (18-64 years) From 65-84 years 85 years and over			
Age continuous Units: years			
median	45		
full range (min-max)	18 to 81		
Gender categorical Units: Subjects			
Female	98		
Male	108		
Arthritis classification Units: Subjects			
Poly-articular	149		
Oligo-articular	57		

End points

End points reporting groups

Reporting group title	Intensive Management

Reporting group description:

First Line Therapy: Methotrexate (12 weeks minimum treatment before next line treatment can start, unless not tolerated). Second Line Therapy: Methotrexate plus Sulfasalazine (12 weeks minimum treatment before next line treatment can start, unless not tolerated). Third Line Therapy Methotrexate plus Leflunomide OR Cyclosporin OR Anti TNF therapy (Etanercept, Infliximab OR Adalimumab) (12 weeks minimum treatment before alternative third line therapy can start). Decision for order of third line therapy was that of the clinician based on clinical contraindications and NICE Guidance.

Reporting group title	Standard Therapy

Reporting group description:

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.

Subject analysis set title	Intention-to-treat
Subject analysis set type	Intention-to-treat

Subject analysis set description:

The ITT population is defined all randomised patients, regardless of if they are ineligible, withdraw, don't comply with the protocol, are lost to follow-up or don't receive any study treatment.

Primary: ACR20

End point title	ACR20

End point description:

The ACR 20 (American College of Rheumatology) response is a composite response measure developed for Rheumatoid Arthritis. To achieve an ACR 20, patients must demonstrate a relative improvement from baseline to 48 weeks of at least 20% in both the tender and swollen joint counts as well as a relative 20% improvement in 3 out of 5 following criteria (33):
- patient global assessment of disease activity (measured by the VAS scale)
- physician global assessment of disease activity (measured by the VAS scale)
- patient assessment of pain (measured by the VAS scale)
- patient assessment of physical function (measured by HAQ)
- inflammatory marker (erythrocyte sedimentation rate (ESR) or C-reactive protein (CRP))

End point type	Primary

End point timeframe:

48 weeks post-randomisation

End point values	Intensive Management	Standard Therapy	Intention-to-treat	
Subject group type	Reporting group	Reporting group	Subject analysis set	
Number of subjects analysed	89[1]	84[2]	173[3]	
Units: Proportion				
Yes	55	37	92	
No	34	47	81	

Notes:

[1] - Before any imputation, ACR20 response data was available for 89 patients in the IM arm.

[2] - Before any imputation, ACR20 response data was available for 84 patients in the StdC arm.

[3] - Before any imputation, ACR20 response data was available for 173 patients in the trial population.

Statistical analyses

Statistical analysis title	Primary endpoint analysis

Statistical analysis description:

Treatment groups will be compared by fitting a multiple logistic regression model to the ACR20 response variable, achieved ACR20 at 48 weeks, adjusted for the minimisation factors (arthritis classification and centre). Treatment and covariate estimates and odds ratios with corresponding 95% confidence intervals (CIs) will be presented, along with the p-values.

Comparison groups	Intensive Management v Standard Therapy
Number of subjects included in analysis	173
Analysis specification	Pre-specified
Analysis type	superiority[4]
P-value	≤ 0.05
Method	Regression, Logistic
Parameter estimate	Odds ratio (OR)
Point estimate	1.91
Confidence interval	
level	95 %
sides	2-sided
lower limit	1.03
upper limit	3.55
Variability estimate	Standard error of the mean
Dispersion value	0.31

Notes:

[4] - The primary endpoint analysis was performed on the full trial population of 206 patients, after multiple imputation was used to impute missing ACR20 component data.

Adverse events

Adverse events information[1]	
Timeframe for reporting adverse events: AEs and SAEs should be monitored from time of patient randomisation until 30 days following the last administration of protocol treatment.	
Assessment type	Systematic

Dictionary used	
Dictionary name	Body system coding
Dictionary version	n/a

Frequency threshold for reporting non-serious adverse events: 0 %

Notes:

[1] - There are no non-serious adverse events recorded for these results. It is expected that there will be at least one non-serious adverse event reported.
Justification: See attached end of trial report submitted to the MHRA for details of adverse events. Leeds Institute of Clinical Trials Research is an academic trials unit where full MedDRA coding is not the standard. It has therefore not been possible for adverse event data to be accurately entered into the full data view within EudraCT as all mandatory categories cannot be completed.

More information

Substantial protocol amendments (globally)

Were there any global substantial amendments to the protocol? Yes

Date	Amendment
08 September 2008	Optional biomarker substudy added: An optional additional 12 mls of blood from consenting patients to be taken at the 3 monthly assessment visit and used for biomarker analysis. Addition to the protocol to allow for additional scanning (ultrasound and MRI) to be performed if local steroid injections are performed into actively swollen joints or tendons.
09 February 2009	Addition of a cost effectiveness measure: In addition to the questionnaires completed by patients at 3 monthly intervals, to collect data on cost-effectiveness (EQ5D or EuroQOL questionnaire and a patient cost questionnaire).
15 July 2009	Optional sub-study added: imaging of 40 control subjects (20 healthy controls and 20 patients with psoriasis only) to provide comparable information regarding imaging findings. To allow accurate interpretation of the imaging findings in the study patients.
19 October 2009	3 changes to the protocol: 1. Section 3.1.1.1 (page 12) amended to state that patients can be treated with either oral or parenteral methotrexate. Some patients experience side effects related to taking oral methotrexate. Parenteral dosing can be used to avoid gastro-intestinal side effects related to the tablets. In such circumstances, we would like to be able to switch patients from oral to parenteral methotrexate. The same doses and drug safety monitoring regime will be followed. Parenteral methotrexate will be used if there are contraindications to oral therapy or if it is felt more appropriate for that individual patient. 2. Appendix A – study schedule of events (pages 37-38) changed to remove mention of pregnancy test at screening. This was included in error and is not mentioned in the text of the protocol. Text of section 6.1 clearly states that urinalysis will be performed to exclude infection at screening, but pregnancy test is not routinely performed. Pregnancy test is not indicated prior to MTX 3. Section 7.7 (page 24) a new section 7.8 (page 24) has been added to detail how the new telephone randomisation system will be operated with the trial opening at multiple sites.

30 April 2010	Changes as a result of the management of the trial being taken over by the Clinical Trials and Research Unit at the University of Leeds. 1. Change of Chief Investigator 2. Change of person named as Applicant on CTA 3. Sample size increased 4. Overall changes to bring protocol in line with CTRU SOPs/Guidelines 5. Study aims, objectives and endpoints sections expanded. 6. Deletion of one of the inclusion criteria 7. Statement of provision for physical and mentally incapacitated patients added to the protocol and Patient Information 8. Change to end of trial definition 9. Overall changes to bring Patient Information Sheet and Informed Consent Document in line with CTRU SOPs/Guidelines and the Imaging SubStudy 10. Overall changes to bring GP Letter in line with CTRU SOPs/Guidelines and the Imaging SubStudy 11. Addendum to all previous and current Patient Information Sheet and Informed Consent Document to obtain permission from patients who have already completed protocol treatment to share their data with the Funders for on going safety reporting and to be able to use their data and samples collected centrally for future research subject to ethical approval.
09 January 2012	1. Addition of a patient ID card. 2. Amendments to the protocol: i. Change to section 8.1 to clarify the duration for which precautions should be used after the last dose of protocol treatment for WCBP or men whose partners are WCBP. ii. New wording regarding the extension to recruitment approved by Arthritis Research UK. iii. Change to the number of months prior to screening which a normal chest x-ray can be accepted without repetition iv. Specification of an additional reason why treatment may be modified or delayed v. New wording to indicate the tests for which it is acceptable to use the results if they are conducted more than 28 days before screening. vi. Addition of a definition of partial response. vii. Amendment to protocol to reflect the revised timelines agreed for reporting to the DMEC committee.

Notes:

Interruptions (globally)

Were there any global interruptions to the trial? No

Limitations and caveats

None reported