

ANNUAL PROGRESS REPORT TO MAIN RESEARCH ETHICS COMMITTEE (For all studies except clinical trials of investigational medicinal products)

To be completed in typescript and submitted to the main REC by the Chief Investigator. For questions with Yes/No options please indicate answer in bold type.

1. Details of Chief Investigator

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2. Details of study

Full title of study:	Prospective Observational Study of the long term hazards of anti-TNF therapy in rheumatoid arthritis
Name of main REC:	NRES Committee Northwest - Haydock
REC reference number:	MREC 00/8/053
Date of favourable ethical opinion:	1st December 2000
Sponsor:	The University of Manchester

3. Commencement and termination dates

Has the study started?	Yes / No
If yes, what was the actual start date?	1 st October 2001
If no, what are the reasons for the study not commencing?	N/A
What is the expected start date?	
Has the study finished?	Yes / No

<p>If yes, complete and submit "Declaration of end of study" form, available at http://www.nres.npsa.nhs.uk/applications/after-ethical-review/endofstudy/</p>	
<p>If no, what is the expected completion date?</p> <p><i>If you expect the study to overrun the planned completion date this should be notified to the main REC for information.</i></p>	<p>Five cohorts are currently open to recruitment:</p> <ul style="list-style-type: none"> i) IL-6 inhibitor cohort ii) Certolizumab cohort iii) Anti-TNF comparison cohort iv) participants starting a biosimilar v) new targeted therapies (including JAK inhibitors) cohort <p>All participants recruited to these cohorts will be followed up for at least 5 years. The current study end date is 30/09/2028.</p>
<p>If you do not expect the study to be completed, give reason(s)</p>	<p><u>N/A</u></p>

4. Registration

<p>Is the study a 'clinical trial'? (Defined as first 4 categories on the IRAS filter page)</p> <p>(For CTIMP please use CTIMP progress reporting template)</p>	<p>Yes / <u>No</u></p>
<p>Is the study registered on a publically accessible database? (Registration of clinical trials is a condition of approval for studies approved after 30 September 2013)</p>	<p>Yes / No <u>N/A</u></p>
<p>If yes, please provide the name of the database and the registration number</p> <p>Database:</p> <p>Registration number: <u>N/A</u></p>	
<p>If no:</p> <p>a. What is the reason for non-registration?</p> <p><u>N/A</u></p> <p>b. What are your intentions for registration?</p> <p><u>N/A</u></p>	

5. Site information

<p>Do you plan to increase the total number of sites proposed for the study?</p> <p>If yes, how many sites do you plan to recruit?</p>	<p><u>Yes</u> / No</p> <p>National study and therefore will permit new centres expressing an interest in participating to join if they treat patients with biologic/other targeted therapies.</p>
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6. Recruitment of participants

In this section, “participants” includes those who will not be approached but whose samples/data will be studied.

<p>Number of participants recruited:</p>	<p><u>Proposed:</u></p> <p>Original Anti-TNF cohort: 16,000 Non-biologic DMARD comparison cohort: 4,000 Mabthera cohort: 1,100 IL-6 inhibitor cohort: 4,000 Cimzia cohort: 2,000 Anti-TNF comparison cohort: 4,000 Biosimilar cohort: 6,000 Other advanced targeted therapies (including JAK inhibitors) cohort: 2000 per drug</p> <p><u>Actual number recruited to date:</u></p> <p>Original Anti-TNF cohort: 15,014 (recruitment now closed) Non-biologic DMARD comparison cohort: 3775 (recruitment now closed) Mabthera cohort: 1,500 (recruitment now closed) IL6 Inhibitor cohort: 1533 Cimzia cohort: 1482 Anti-TNF comparison cohort: 2203 Biosimilar cohort: 2995 Other advanced targeted therapies (including JAK inhibitors) cohort: Olumiant - 260 patients, Xeljanz – 25 patients.</p>
<p>Number of participants completing trial:</p>	<p><u>Actual number completed to date:</u> All participants are being followed-up until at least 2028.</p>
<p>Number of withdrawals from study to date due to:</p> <p>(a) withdrawal of consent – 534 (approx.)(This includes patients who have not withdrawn consent but site has requested to close participation in the study. These patients will still be followed up directly where applicable and via links with national databases) (b) loss to follow-up – 2300 (approx.)(this includes non-biologic patients in our control cohort who then commence a biologic that we are no longer recruiting and therefore cannot be followed any further, as well as patients who move to a new centre who do not participate in the study) (c) death (where not the primary outcome) - 5292</p> <p>Total study withdrawals: 8126 (approx.)</p>	
<p>*Number of treatment failures to date (prior to reaching primary outcome) due to: <u>(N/A – not a trial)</u> (a) adverse events (b) lack of efficacy</p> <p>Total treatment failures:</p>	

* Applies to studies involving clinical treatment only	
Have there been any serious difficulties in recruiting participants?	Yes / No
If Yes, give details:	
Do you plan to increase the planned recruitment of participants into the study? <i>Any increase in planned recruitment should be notified to the main REC as a substantial amendment for ethical review.</i>	Yes / No (unless new targeted therapies for RA are licensed in the UK in the future)

7. Safety of participants

Have there been any related and unexpected serious adverse events (SAEs) in this study?	Yes / No Not Applicable
Have these SAEs been notified to the Committee? <i>If no, please submit details with this report and give reasons for late notification.</i>	Yes / No Not applicable
Have any concerns arisen about the safety of participants in this study? <i>If yes, give details and say how the concerns have been addressed.</i>	Yes / No

8. Amendments

Have any substantial amendments been made to the trial during the year?	Yes / No
If yes, please give the date and amendment number for each substantial amendment made.	Substantial Amendment 26: REC approved 12/10/2018 HRA approved 12/10/2018

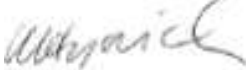
9. Serious breaches of the protocol

Have any serious breaches of the protocol occurred during the year? <i>If Yes, please enclose a report of any serious breaches not already notified to the REC.</i>	Yes / No Yes / No
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10. Other issues

<p>Are there any other developments in the study that you wish to report to the Committee?</p> <p>Are there any ethical issues on which further advice is required?</p> <p><i>If yes to either, please attach separate statement with details.</i></p>	<p style="text-align: right;"><u>Yes</u> / <u>No</u></p> <p>We would like to make the committee aware that development of a study web portal for clinicians/nurses to enter baseline and follow-up data is still ongoing. This will run alongside the original paper based system until fully operational. Any required changes will be presented to the committee as a substantial amendment for approval prior to implementation.</p> <p>We are also still developing a web portal for patients to better communicate news about the study and also to enter follow up data. This will also run alongside the original paper based system. Any required changes will be presented to the committee as a substantial amendment for approval prior to implementation.</p> <p style="text-align: right;">Yes / <u>No</u></p>
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11. Declaration

Signature of Chief Investigator:	
Print name:	Prof. Kimme Hyrich
Date of submission:	08/11/2018