NHS
Health Research Authority

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

If yes, complete and submit "Declaration of end of study" form, available at http://www.nres.npsa.nhs.uk/applications/after-ethical-review/endofstudy/	

If no, what is the expected completion date? *If you expect the study to overrun the planned completion date this should be notified to the main REC for information.*	Five cohorts are currently open to recruitment: 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 All participants recruited to these cohorts will be followed up for at least 5 years. The current study end date is 30/09/2028.
If you do not expect the study to be completed, give reason(s)	***N/A***

4. Registration

Is the study a 'clinical trial'? (Defined as first 4 categories on the IRAS filter page) (For CTIMP please use CTIMP progress reporting template)	*Yes* / ***No***
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)	Yes / No ***N/A***
If yes, please provide the name of the database and the registration number Database: Registration number: ***N/A***	
If no: a. What is the reason for non-registration? ***N/A*** b. What are your intentions for registration? ***N/A***	

5. Site information

Do you plan to increase the total number of sites proposed for the study? If yes, how many sites do you plan to recruit?	***Yes*** / *No* National study and therefore will permit new centres expressing an interest in participating to join if they treat patients with biologic therapy.

6. Recruitment of participants

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

<table>
<tr><td>Number of participants recruited:</td><td><u>Proposed in original application:</u>
16,000 biologic patients , 1,100 rituximab patients, 4000 IL-6 inhibitor cohort patients, 2,000 certolizumab patients, 6,000 biosimilar patients and 4,000 patients to the anti-TNF comparison cohort. In addition to this, there was a recruitment target of 4,000 patients in the non-biologic DMARD comparison cohort.

<u>Actual number recruited to date:</u>
- 15,014 patients to the original anti-TNF cohort (recruitment now closed
- 1,500 rituximab patients (recruitment now closed)
- 3,775 DMARD comparison patients (recruitment now closed)
- 1397 certolizumab patients
- 1367 IL-6 inhibitor cohort patients
- 2116 anti-TNF comparison cohort patients
- 1688 biosimilar patients</td></tr>
<tr><td>Number of participants completing trial:</td><td>Actual number completed to date:
All participants are being followed-up until at least 2028.</td></tr>
<tr><td colspan="2">Number of withdrawals from study to date due to:

(a) withdrawal of consent - 424
(b) loss to follow-up – 2200 (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) - 4866

Total study withdrawals: 7490</td></tr>
<tr><td colspan="2">*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

Total treatment failures:

* Applies to studies involving clinical treatment only</td></tr>
<tr><td>Have there been any serious difficulties in recruiting participants?</td><td>Yes / <u>No</u></td></tr>
<tr><td colspan="2">If Yes, give details:</td></tr>
</table>

Do you plan to increase the planned recruitment of participants into the study? *Any increase in planned recruitment should be notified to the main REC as a substantial amendment for ethical review.*	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*** This is an observational cohort study to monitor long term safety of new therapies for rheumatoid arthritis. It is therefore the responsibility of consultant/nurse to assess causality and report to the regulatory authorities as necessary.
Have these SAEs been notified to the Committee? *If no, please submit details with this report and give reasons for late notification.*	*Yes / No /****Not applicable***
Have any concerns arisen about the safety of participants in this study? *If yes, give details and say how the concerns have been addressed.*	*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.	Date approved: Substantial Amendment 23: REC approved 14/10/2016 HRA approved 02/11/2016 Substantial Amendment 24: REC approved 02/12/2016 HRA approved 14/03/2017 Substantial Amendment 25: REC approved 24/08/2017 HRA approved 24/08/2017

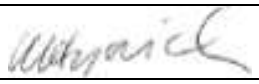
9. Serious breaches of the protocol

Have any serious breaches of the protocol occurred during the year? *If Yes, please enclose a report of any serious breaches not already notified to the REC.*	*Yes / ****No*** *Yes / No*

10. Other issues

Are there any other developments in the study that you wish to report to the Committee?	***Yes*** */ No* 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. 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.
Are there any ethical issues on which further advice is required? *If yes to either, please attach separate statement with details.*	*Yes /* ***No***

11. Declaration

Signature of Chief Investigator:	
Print name:	Prof. Kimme Hyrich
Date of submission:	20/09/2017