Welcome to the Integrated Research Application System

IRAS Project Filter

The integrated dataset required for your project will be created from the answers you give to the following questions. The system will generate only those questions and sections which (a) apply to your study type and (b) are required by the bodies reviewing your study. Please ensure you answer all the questions before proceeding with your applications.

Please enter a short title for this project (maximum 70 characters)
Toxicity from Anti-TNF Therapy

REC details:

Name of main REC:
North West 5 Research Ethics Committee

REC Reference Number:
00/8/53

NRES form lock code:

1. Select one category from the list below:

- ○ Clinical trial of an investigational medicinal product
- ○ Study only involving data or tissues not identifiable to the researcher

If your work does not fit any of these categories, select the option below:

- ◉ Other study

2. Does the study involve the use of any ionising radiation?

○ Yes ◉ No

3. In which countries of the UK will the research sites be located?*(Tick all that apply)*

- ☑ England
- ☑ Scotland
- ☑ Wales
- ☑ Northern Ireland

3a. In which country of the UK will the lead NHS R&D office be located:

- ◉ England
- ○ Scotland
- ○ Wales
- ○ Northern Ireland
- ○ This study does not involve the NHS

4. Do you plan to include any participants who are children?

○ Yes ◉ No

5. Do you plan to include any participants who are adults unable to consent for themselves through physical or mental incapacity?

○ Yes ◉ No

Answer Yes if you plan to recruit living participants aged 16 or over who lack capacity, or to retain them in the study following loss of capacity. Intrusive research means any research with the living requiring consent in law. This includes use of identifiable tissue samples or personal information, except where application is being made to the NIGB Ethics and Confidentiality Committee to set aside the common law duty of confidentiality in England and Wales. Please consult the guidance notes for further information on the legal frameworks for research involving adults lacking capacity in the UK.

6. Is the study or any part of it being undertaken as an educational project?

○ Yes ◉ No

NOTICE OF SUBSTANTIAL AMENDMENT
Please use this form to notify the main REC of substantial amendments to all research other than clinical trials of investigational medicinal products (CTIMPs).
The form should be completed by the Chief Investigator using language comprehensible to a lay person.

Details of Chief Investigator:

	Title	Forename/Initials	Surname
	Prof	Deborah	Symmons
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Full title of study:	Prospective observational study of the long term hazards of anti-TNF therapy in rheumatoid arthritis
Lead sponsor:	University of Manchester
Name of REC:	North West 5 Research Ethics Committee
REC reference number:	00/8/53
Name of lead R&D office:	Central Manchester University Hospitals NHS Foundation Trust
Date study commenced:	01/12/2000 (date of original ethical approval)
Protocol reference (if applicable), current version and date:	Main protocol dated 06/10/2003. Two current substudy protocols: 1) certolozimab and anti-TNF (v3: 15/10/2010) 2) tocilizumab (v1.1: 17/01/2011)
Amendment number and date:	Amendment 20: 16/02/2015

Type of amendment

(a) Amendment to information previously given in IRAS

(●) Yes ( ) No

If yes, please refer to relevant sections of IRAS in the "summary of changes" below.

(b) Amendment to the protocol

( ) Yes (●) No

If yes, please submit either the revised protocol with a new version number and date, highlighting changes in bold, or a document listing the changes and giving both the previous and revised text.

(c) Amendment to the information sheet(s) and consent form(s) for participants, or to any other supporting

documentation for the study

○ Yes ◉ No

If yes, please submit all revised documents with new version numbers and dates, highlighting new text in bold.

Is this a modified version of an amendment previously notified and not approved?

○ Yes ○ No

If yes, please explain the modifications made under "Summary of changes" below

Summary of changes

Briefly summarise the main changes proposed in this amendment. Explain the purpose of the changes and their significance for the study.
If the amendment significantly alters the research design or methodology, or could otherwise affect the scientific value of the study, supporting scientific information should be given (or enclosed separately). Indicate whether or not additional scientific critique has been obtained.

This amendment covers (i) the addition of biosimilar drugs to the BSRBR-RA study and, (ii) increase in size of the anti-TNF comparison cohort.

(i) Addition of biosimilars to the study

The BSRBR-RA has been collecting observational cohort data on patients receiving biologic therapy for rheumatoid arthritis for nearly 15 years in the UK. Biological medicines are made from living organisms using biotechnology techniques. Many of these original biologic therapies are now reaching the end of their patents. This means that other manufacturers are now able to make similar versions of these drugs called "biosimilars". These drugs have a complex manufacturing process and therefore are not generic because they are not identical to the original biologic drug. Thus, the introduction of biosimilars into the treatment pathway for rheumatoid arthritis could potentially raise different safety concerns.

Currently there are two biosimilar medicines approved for use by the European Medicines Agency (EMA) in the UK. These biosimilars are based on infliximab (trade names Remsima and Inflectra) and it is envisaged that these will be introduced to the UK in early 2015. Clinical trial data has shown these medicines to be similar in terms of short-term equivalence in comparison with the originator drug infliximab in patients with rheumatoid arthritis1. However, the EMA have labelled these medicines as requiring "additional monitoring" whilst being used in routine clinical care. This means the medicines are being monitored even more intensively than other medicines because there is less information available on them compared to other medicines2. The EMA have also recommended that the companies who hold the manufacturing authorisation for these drugs should participate in existing pharmacoepidemiological studies including registries and population based databases which are already in place for the reference product 3, 4. Finally, the EMA have outlined a concern regarding the definite identification of these drugs as being particularly important due to the difference in manufacturing process compared to the originators. Thus they have recommended that measures should be taken to identify clearly any biological medicinal product under "additional monitoring" with regards to the name and batch number of the product4.

Therefore, as the national observational study for monitoring the use of biologic therapies in the UK, the BSRBR-RA would like to propose to recruit a new cohort of patients starting these biosimilar medicines for rheumatoid arthritis as they become licensed for use in the UK. As outlined, we are currently recruiting patients starting the originators but we plan to extend this to capture the full range of formulations available. However, it is very difficult to predict sample size as the drugs are not yet to market and the market share is not yet set but we envision this might extend to 2000 patients over the first 3-5 years of study. In terms of additional data collection, we propose to collect the batch number and trade names of the biosimilars on the baseline and follow-up data collection forms (see attached) in order to ensure we are correctly identifying these drugs.

Representatives from the National Rheumatoid Arthritis Society (NRAS), who describe themselves as 'the voice of people affected by rheumatoid arthritis' have also published a position paper on biosimilar medicines and have recommended that all manufacturers of biosimilars should support the BSRBR-RA so that the same level of safety monitoring can be carried out on biosimilars as there as been for the originator biologics (see NRAS Position Statement).

(ii) Increase in the size of the anti-TNF comparison cohort

The most appropriate comparison cohort for the biosimilar medicines will be the originator biologics. We are already

recruiting a comparison cohort of 2000 patients staring the originator drugs and we have recruited 1250 patients to this cohort to date. We would like to increase the sample size of the anti-TNF cohort to 4000 patients to allow us to recruit a contemporary cohort of anti-TNF patients enrolled in the study at the same time as the biosimilar cohort are recruited as we have already demonstrated that the disease characteristics of these patients exposed to these therapies changes over time5. Funding and resources are in place to accommodate this increase in cohort size.

References
1Yoo et al. Ann Rheum Dis. 2013 Oct;72(10):1613-20.
2EMA/244682/2013; Medicines under additional monitoring. Committee for Medicinal Products for Human Use (CHMP), 2013.
3EMEA/CHMP/BMWP/42832/2005 Rev1; Guideline on similar biological medicinal products containing biotechnology-derived proteins as active substance: non-clinical and clinical issues. Committee for Medicinal Products for Human Use (CHMP), 2014.
4EMA/CHMP/BMWP/403543/2010; Guideline on similar biological medicinal products containing monoclonal antibodies – non-clinical and clinical issues. Committee for Medicinal Products for Human Use (CHMP), 2012.
5Hyrich KL, Watson KD, Lunt M, Symmons DP; British Society for Rheumatology Biologics Register (BSRBR).Changes in disease characteristics and response rates among patients in the United Kingdom starting anti-tumour necrosis factor therapy for rheumatoid arthritis between 2001 and 2008. Rheumatology (Oxford). 2011 Jan;50(1):117-23.

Any other relevant information

Applicants may indicate any specific issues relating to the amendment, on which the opinion of a reviewing body is sought.

List of enclosed documents

Document	*Version*	*Date*
Clinical Follow Up form	11	16/02/2015
ClinicalBaseline form	11	16/02/2015
NRAS Position Statement on Biosimilar Medicines	N/A	14/08/2014

Declaration by Chief Investigator

1. *I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.*
2. *I consider that it would be reasonable for the proposed amendment to be implemented.*

Date of submission:.....

Signature:.....

Declaration by the sponsor's representative

I confirm the sponsor's support for this substantial amendment.

Signature: .....

Print Name:

Post:

Organisation:

Date: *(dd/mm/yyyy)*

Does this amendment involve new types of exposure or increased exposure to ionising radiation?

◯ Yes ◯ No

If Yes, please provide details below:

Does this amendment involve inclusion of adults lacking capacity or a change to the arrangements relating to adults lacking capacity?

○ Yes ○ No

If Yes, please provide details below:

Declaration by Sponsor's Representative

This section was signed electronically by Lynne MacRae on 27/02/2015 13:58.

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