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 complete the questions in order. If you change the response to a question, please select 'Save' and review all the questions as your change may have affected subsequent questions.

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 Confidentiality Advisory Group 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
Work Address	Arthritis Research UK Epidemiology Unit, 2nd Floor Stopford Bldg, Oxford Road, Manchester
PostCode	M13 9PL
Email	deborah.symmons@manchester.ac.uk
Telephone	01612755044
Fax	01612751640

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 sub-study protocols: 1) certolizumab and anti-TNF (v3: 15/10/2010) tocilizumab (v1.1: 17/01/2011)
Amendment number and date:	Amendment 22: 07/07/2016

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 <u>either</u> 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 3 main points:

i) Change of Chief Investigator
ii). An extension of the study recruitment and follow up period
iii). Changes to BSRBR-RA Short baseline form/Clinical follow-up form/Clinical baseline form

i) Change of Chief Investigator

The BSRBR-RA would like to update the Chief Investigator details relating to this study. Professor Deborah Symmons has recently retired from the university. Although she will remain peripherally involved in the study, we would like to remove Deborah as Chief Investigator and replace her with Professor Kimme Hyrich (C.V. enclosed), who, prior to this, was previously a Principle Investigator on the study since 2007.

ii) Extension of the study recruitment and follow up period

Background and Rationale:

The BSRBR-RA is regarded as the gold standard pharmacovigilance registry for rheumatoid arthritis nationally and internationally and both the National Institute for Healthcare and Clinical Excellence (NICE) and the British Society for Rheumatology (BSR) guidance recommend that all patients treated with biologic therapies are registered for long-term follow-up in the study to monitor the safety of these new drugs.

The BSRBR-RA has been recruiting and following patients receiving biologic and conventional therapy for rheumatic diseases since October 2001. The current protocol states that all patients are actively followed via the clinical using questionnaires for a period of at least five years from registration and via the patients themselves for three years. All patients in the register are also flagged with the Health & Social Care Information Centre (HSCIC) for life-long follow-up so the study team are informed when a participants develops cancer or dies.

The initial 'extension to follow up' amendment (which was approved on 06/05/2008) proposed the extension of the clinical follow up of all patients until 2013 to enable the BSRBR-RA to use the data sent by the HSCIC in drug-specific analysis past the first five years of follow-up. In addition, it also enabled the study to consider the risk of other more latent serious adverse events, such as cancer, past the initial five years.

There are an increasing number of new biosimilar therapies becoming available for the management of rheumatoid arthritis. The National Rheumatoid Arthritis Society (NRAS) recommends that all manufacturers of biosimilars subscribe to the British Society for Rheumatology Biologics Registers so that pharmacovigilance protocols are the same as those of the original biologics and long term safety data is properly collected. This view has been echoed by

the Association of British Pharmaceutical Industries (ABPI) and by the British Society for Rheumatology (BSR).

The 'second extension to follow up' amendment which was approved on 13/06/2012 stated that all BSRBR-RA participants would be followed up via their rheumatologist until the end of the study in 2018. However, since then, additional cohorts have been opened up to recruit these newly introduced biosimilars to the BSRBR-RA, starting with the infliximab biosimilars Remsima and Inflectra, and going on to include the etanercept biosimilar Benepali (as well as other biosimilar treatments introduced in the UK in the future to treat rheumatoid arthritis). The 'Biosimilars' amendment (substantial amendment 20) approved on 16/03/2015 covered the introduction of all biosimilar drugs to the study. However, in order to facilitate inclusion of these treatments in the BSRBR-RA using the current study design, we propose extending the study end date for a further 10 years to 30/09/2028.

As the participants consented to be involved in the study for at least five years (as stated in the patient information sheet v7) there is no requirement to re-consent existing patients.

iii) Revisions to BSRBR-RA Clinical baseline form/Clinical follow-up form/Short baseline form

The BSRBR-RA clinical baseline and clinical follow up forms have been updated to capture information regarding low disease activity when a DAS-28 score might not be available. This is particularly important for patients who might be switching to a biosimilar as a DAS-28 measurement is not always completed and a measure of disease activity at the time of switch will be essential in interpreting the data. There have also been several formatting/administrative changes to these forms.

Full details of these changes are outlined below:

Clinical baseline form v11.1(07-07-2016)
- Added low disease activity question
- Added biosimilar trade names
- Removed drugs that are no longer being registered
- Formatting changes made to biosimilar switching question to make it clearer
- Steroids question corrected (used to read if receiving oral steroids and then ask if IV/SC)
- Date for Zoster vaccine

Clinical follow-up form v11.2 (07/07/2016)

- Added 'trade name' where needed
- New column with low disease activity question
- Changed point 2 on re-registration checklist to accommodate lack of DAS
- Added new biosimilars to infusion list
- Changed Infliximab infusion reaction in ESI list to Serious Drug Hypersensitivity

The BSRBR-RA short baseline form has also undergone some formatting changes and been updated to collect information relating to TB screening/herpes zoster vaccine to bring it in line with our existing BSRBR-RA consultant baseline where we already routinely collect this information. This new short baseline form will replace both the current short baseline form (Version 1: 04/11/2010) and the comparison cohort switch form (Version 2: 08/02/2011).

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	11.2	07/07/2016

Clinician Baseline Form	11.1	07/07/2016
Short Baseline Form	3	06/04/2016
KLH CV	N/A	23/05/2016

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: 18/07/16

Signature: [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 14/07/2016 13:38.

Job Title/Post:	Faculty Research Practice Coordinator
Organisation:	University of Manchester
Email:	lynne.macrae@manchester.ac.uk