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 Kimme Hyrich
Work Address	Arthritis Research UK Centre for Epidemiology
	Unit, 2nd Floor Stopford Bldg,
	Oxford Road, Manchester
PostCode	M13 9PL
Email	kimme.hyrich@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 24: 26/10/2016

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 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 substantial amendment consists of two parts:

(i) New version of the Participant Information Sheet and Consent Form for registering new participants in the study (version 8.0, dated 19/10/2016).

The BSRBR-RA study started in 2001 and was only expected to run for 5 years to monitor the safety of the new biological drugs prescribed for rheumatoid arthritis in routine NHS clinical care.

As newer biological drugs were licensed and approved in the UK, the BSRBR-RA was extended to include these and also follow-up of the original biological drugs was lengthened to monitor the longer term safety of these drugs to study outcomes such as cancer and death. We continue to secure funding to continue this study to capture long-term follow-up data on these drugs and the current end date is 30/09/2028.

In light of the long-term sustainability of the study, we felt it was timely to bring the BSRBR-RA Participant Information Sheet and Consent Form in line with current regulations around data protection, electronic data capture methods and fair processing, data security and informed consent for medical research.

If approved, this new version of the consent form/participant information sheet will be strictly version controlled in the BSRBR-RA database to ensure we are fully aware of which participants have consented to the new version.

The main changes we have made to Version 8 (dated 19/10/2016) of the Participant Information Sheet and Consent Form are listed below:

1. We include more information about the conditions of data processing:

a. We have been specific about which items of personal identifiable data are shared with other organisations and for what purpose.
b. We have listed the organisations that we currently share personal identifiable information with.
c. We have given more information about why we need to link individual healthcare records with other national databases such as NHS Digital. We have listed some of these organisations in both the Consent Form and Participant Information Sheet, with a full list provided on the website.
d. As the study will continue for a number of years, we have outlined that approved third party data processors may also have access to personal identifiable data in order to process the data for study purposes only, where legal agreements are in place between the parties.

2. We have outlined the organisations currently involved in the data processing activities.

3. We have included a section on the risks and benefits of participating in the research study.

4. We have stated how long the data will kept for at the end of the study.

5. We have outlined how the results of the study will be communicated to participants and healthcare professionals.

6. We have extended the section on data security, data protection and data confidentiality.

7. We have extended the section on withdrawal of consent to outline three clear options available to participants, with details of who to contact should they wish to withdraw from the study.

8. We have included a link to the study website, where participants can read further information including lay summaries of results and publications from the study to date.

9. We have included details of who to contact should participants have concerns or complaints about the study.

10. Due to the fact that the Participant Information Sheet is now 5 pages long, we have included a table of contents on the first page to make it easier to navigate/find the questions that potential participants are interested in.

This new version (V8.0, dated 19/10/2016) of the Participant Information Sheet and Consent Form has been reviewed by members of the public and patients with rheumatoid arthritis who are members of the Centre for Epidemiology Research User Group (RUG) at The University of Manchester. They felt it was "easy to understand the medical content" and "explained the study very well".

(ii) Applying for a Section 251 exemption for existing participants in the study to share data with trusted third parties for data processing activities related to the study.

The current version of the consent form (v7, dated 23/07/2010) states:

"Identifiable information about you will be held by the research team at Manchester University Medical School and the National Health Service Information Centre..."

We therefore need explicit consent to share this data with trusted third parties for data processing purposes, as (i) we are in the process of designing a web-based data collection portal which may be developed by a trusted third party provider (where appropriate legal agreements are in place) and (ii) we would like to link the BSRBR-RA data to other national databases included the Hospital Episodes Statistics (HES - HSCIC/NHS Digital) and MINAP (Myocardial Ischaemia National Audit Project – NICOR/HQIP) to further enrich the data we currently hold.

There are currently 22,000 participants in the study at 250+ NHS hospitals and, due to the fact that some of these participants will no longer be under active follow-up for a number of reasons, it would not be possible to go back and re-consent these participants with proposed version 8.0 (dated 19/10/2016) of the Participant Information Sheet /Consent Form. If we were to attempt to re-consent all patients in the study to share personal data with a third party processor/link to national databases such as HES/MINAP, this would have a number of implications that would be detrimental to the study for logistical and epidemiological reasons including:

• Data could not be shared with a third party processor until all participants in the study had re-consented. Experience from a similar, but albeit much smaller study (~only 5% the size of the BSRBR-RA) has shown this takes a significant time (2 years+) with the loss of many participants in the study (around 30%). The mechanisms to do this are also unclear but could include a significant burden to NHS trusts where >500 participants in a single centre may need to be re-consented. Doing so directly with participants by post is unlikely to be successful, as at best 70% of participants are likely to return forms to studies.

• Where participants do not consent (or do not reply to the request to re-consent) to the data sharing, they would need to be removed from the database and follow-up stopped. Participants, who respond to questionnaires especially when posted, tend to have a different disease severity than those who do not. This is a well-recognised phenomenon in observational research and the BSRBR-RA is unfortunately no different. Our experience with the other, much smaller study, where re-consent was needed for a different reason (not to move data), has shown that participants who did re-consent had a very different disease severity than those who did not. To exclude these participants from our study would be catastrophic in terms of the introduction of significant bias going forward and compromise to the study validity.

Therefore we would like to seek initial approval from the ethics committee to submit an application to the Confidential Advisory Group for a Section 251 exemption to share the data with trusted third party processors for these two purposes for existing participants in the study. If approved by the ethics committee, we will then proceed to submit a section 251 exemption to the CAG.

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*
BSRBR-RA Consent Form	8	19/10/2016
BSRBR-RA Participant Information Sheet	8	19/10/2016

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: 7.11.16

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 04/11/2016 12:21.

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