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
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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:	Manchester University 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) 2) tocilizumab (v1.1: 17/01/2011)
Amendment number and date:	Substantial Amendment 27 (06/12/2018)

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 three main areas (i) electronic data collection in the BSRBR via the BSRBR-RA Web System, (ii) introduction of new supporting documentation to supplement the launch of the BSRBR-RA web system and (iii) changes to the BSRBR-RA main study protocol.

i) Electronic Data Collection – The BSRBR-RA web system
Background
The British Society for Rheumatology Biologics Register - Rheumatoid Arthritis (BSRBR-RA) currently collects data from clinical rheumatology teams based at hospitals across the UK using paper-based forms. These data are currently entered onto a Microsoft Access database (which was originally built in 2001) by a team of researchers at the Biologic Studies Group offices at The University of Manchester.

This system needs replacing with an electronic web system (or portal) for many reasons including:

For efficiency for both the clinical teams and the BSRBR-RA administration team. The new system will save both time and important resource to both.
For transparency so the clinical teams can access the patient data for the study and see what information was last recorded. This will ensure better data quality.
Reducing the amount of personal data transferred by post and the costs associated with this.
Long-term sustainability of the study.

The BSRBR-RA originally sought and received approval, to collect data electronically as part of Substantial Amendment 14, approved by the REC on 10/09/2010. Unfortunately, as is the case with many complex IT systems, this was not possible at the time. A number of attempts since this with external suppliers have also failed.

Over the past 12 months, the study funder (the British Society for Rheumatology) agreed that we could develop the system in-house at the University based on a very successful and widely accepted similar system, the BADBIR clinical portal, which has been in use at all NHS hospitals across the UK and ROI in dermatology departments for over 7 years. The system was designed and built by the University of Manchester.

Scope of the BSRBR-RA web system

The BSRBR-RA web system will be a web based, access managed, secure system hosted on University of Manchester virtual secure servers. This new system is intended to streamline the process of data collection and make it more secure, more auditable and more environmentally friendly by reducing the need of printing and postage between the study office and over 150 clinical sites.

Clinical staff at over 150 centres that recruit and follow up patients in BSRBR-RA will use the web interface to log in to their restricted area, enter all the information that BSRBR-RA requires on registered patients and communicate with the study staff regarding patient information. The pharmacovigilance team at the study office will be able to process adverse events more efficiently by using automated and guided processes. Once deployed, the new web system will replace the locally used Microsoft Access interface for data entry and pharmacovigilance. Some level of backward

compatibility will be provided for other components that connect to the current system.

The BSRBR-RA web system will make the process of migration to the new system gradual and reversible for the clinical staff. Furthermore, the new system will incorporate a more secure system architecture to handle sensitive and personal information and make use of encryption in transit, encryption at rest and secure web authentication.

The new system will also allow for better scalability and future development.

Proposed implementation

Moving to a web based system will be a staged process and we propose to test the new system internally first before migrating the data and testing at a small number of pilot site hospitals. These sites will be chosen from a mixture of participating sites of different sizes/types with differing needs/levels of capacity to make sure the new system fulfils their requirements. The data collection forms remain the same as they currently are and there is no change to the paper-based data collection process to study participants. Following a successful pilot stage, the BSRBR-RA web system will be expanded to include all centres.

Frequent input and feedback from end-users will be vital to the success of this system.

Access Control

It is intended that the web system will be accessible via a link on the BSRBR-RA website (www.bsrbr.org).

In line with GCP requirements, the PI at every centre is responsible for keeping an up to date delegation log. Having a delegation log integrated within the web based system will allow this to be done in a seamless manner as controlling access to the web based system will be integrated with delegation. It also enables the study staff to conduct quick and efficient site file audits.

Study participants will be assigned to sites/centres and all web requests to access patient information check that the user has been assigned to the patient's centre. Thus, clinicians/nurses can only access their own patients' records. Web sessions expire after 15 minutes of no activity. User accounts are locked if they have not logged into the system for 6 months or 5 incorrect password attempts.

System Security

The purpose of the system is to enable users to perform most of their day to day tasks in relation to the study on one web-based system. In addition to eradicating the reliance on physical post and paper-based incoming data, the system will also bolster the security of data in line with the current guidelines of handling sensitive and personal data.

It is imperative that the system design complies with the security requirements related to the nature of data it must hold. Protecting patients' personal identifiably data is of paramount importance. The web application is available to authenticated users from any internet connection but the connection is secured using HTTPS which is at least 128 bit encryption. All data that could be used to identify a study participant (excluding date of birth and gender) is encrypted when entered into the web application and before it is saved to the database and 256-bit encryption is used to secure this information.

As detailed above, each new user will be verified by the BSRBR-RA before any encrypted information is transferred, ensuring that only approved individuals are able to use the system. Each recruiting centre that enters data onto the database will be able to view the information that they have entered themselves, but not any data that has been input by any other centre, unless a patient's care is transferred to another participating site. Should this occur, the BSRBR-RA will seek permission from the participant's previous site to allow data provided by them to be accessible by the named individuals working on the study at the new site. The BSRBR Team will be able to view all the information that has been entered by any centre.

All aspects of security for this new system are covered in the BSRBR-RA System Level Security Policy Version 1, Dated 5th December 2018 (see section (ii)).

ii) Introduction of supporting documentation for the BSRBR-RA web system

The BSRBR-RA would like to introduce the following documents to assist with the implementation of the BSRBR-RA web system:

a) BSRBR-RA System Level Security Policy v1, 05/12/2018

This document provides detailed technical information relating to all aspects of BSRBR-RA web system infrastructure and security. It also includes information regarding current University of Manchester (study sponsor) IT Policies and a list of participating NHS trusts.

b) BSRBR-RA Stakeholder Responsibilities Document v1, 05/12/2018

This document outlines the accountabilities and responsibilities of all stakeholders in the BSRBR-RA to assist the continued successful operation of the study and the safety of participants and aid with the setting up of site agreements at participating NHS trusts.

iii) Re-design of the main BSRBR-RA study protocol

The BSRBR-RA main study protocol has been amended and re-designed for the following reasons:

a) To incorporate and replace previous sub-study protocols for the Tocilizumab and Certolizumab cohorts which has previously caused confusion as the study has evolved over the 17 year period it has been running.

The BSRBR-RA main Study Protocol v2.0 (05/12/2018) will supersede the following documents:

BSRBR-RA Main study protocol – 06/10/2003.
BSRBR-RA Tocilizumab sub study protocol – v1.1, 17/01/2011.
BSRBR-RA Certolizumab sub study protocol – v3.0, 15/11/2010.

b) To incorporate the inclusion of new types of drugs in the study including biosimilars (approved as part of substantial amendment 20 on 16/03/2015) and JAKi.(approved as part of substantial amendment 25 on 24/08/2017).

For example:

The current BSRBR Main study protocol (06/10/2003) states:

“The study proposed is a series of prospective cohort studies comparing the risk of development, over 5 years, of the endpoint between: (i) an exposed group of patients with one of a list of defined rheumatic disorders newly exposed to a biologic drug and (ii) a comparison cohort of patients with similar disease characteristics exposed to other, but non-biologic, therapies..”

Whereas ‘BSRBR-RA Study Protocol v2.0 (05/12/2018)’ states:

“The study proposed is a prospective cohort study comparing the risk of development of adverse outcomes over at least 5 years between a recruited group of patients with RA who are recipients of a new biologic, biosimilar or other new advanced targeted therapy and appropriate comparison cohorts of patients with similar disease characteristics including those receiving established TNFi therapies and csDMARD therapy who are biologic naive.”

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 Study Protocol (Clean)	2.0	05/12/2018
BSRBR-RA Study Protocol (Tracked)	2.0	05/12/2018

BSRBR-RA System Level Security Policy (SLSP)	1.0	05/12/2018
BSRBR-RA Stakeholders Responsibilities	1.0	05/12/2018

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:.....12/12/2018.....

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 Mrs Stacey Body on 12/12/2018 09:26.

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