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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	2nd Floor Stopford Bldg,		
	Oxford Road, Manchester		
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Telephone	01612755044		
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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 sub-study protocols: 1) certolizumab and anti-TNF (v3: 15/10/2010) tocilizumab (v1.1: 17/01/2011)
Amendment number and date:	Amendment 25: 17/07/2017

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 4 main points:

I. Addition of a new "Janus kinase inhibitor and targeted therapies" cohort.
II. Increase in the size of existing cohorts.
III. Introduction of an outreach study invitation letter aimed at patients being re-registered.
IV. Revisions to the following BSRBR-RA study documents:

BSRBR-RA Participant Information Sheet (updated to v9.0 - 17/07/2017)
BSRBR-RA Consent Form (updated to v9.0 - 17/07/2017)
BSRBR-RA Outreach Consent Invitation Letter (updated to v1.1 - 17/07/2017)
BSRBR-RA Clinical Baseline Form (updated to v11.2 - 17/07/2017)
BSRBR-RA Short Baseline Form (updated to v3.1 - 17/07/2017)
BSRBR-RA Clinical Follow-Up Form (updated to v11.3 - 17/07/2017)
BSRBR-RA Patient Baseline Questionnaire (updated to v5.0 - 17/07/2017)
BSRBR-RA Patient 6 Monthly Follow-up Questionnaire (updated to v7.0 - 17/07/2017)
BSRBR-RA Poster for Patient Recruitment (updated to v2.0 - 17/07/2017)

I. Addition of new targeted therapies including JAK inhibitors to the BSRBR-RA study

The BSRBR-RA has been collecting observational cohort data on patients receiving biologic therapy for rheumatoid arthritis in the UK for over 15 years. Biologic DMARDS (bDMARDS), including the TNF inhibitors (TNFi including Enbrel, Remicade, Humira), first became available to treat RA in the late 1990's, having a profound effect on the outcome of many patients with RA. In 2001, the BSRBR-RA was set up to monitor the long-term effects of these drugs. Since then, newer advanced therapies have been developed based on this knowledge. These later drugs included the IL-6 inhibitors (RoActemra) and biosimilars (Inflectra, Remsima, Benepali, Flixabi) which were also added as new cohorts to the BSRBR-RA study.

Now a newer class of these bDMARDS is available to use in the RA treatment pathway and these include the Janus kinase (JAK) inhibitors (Tofacitinib and Baricitinib), with more in the pipeline. The JAK inhibitors are small molecules which are administered orally to patients. These new drugs have proven safety and efficacy in clinical trials in the short-term, but there is no long-term observational data when used in the clinical setting. The drugs also have a different mode of action to the other bDMARDS and therefore may have a different safety profile to that of those already studied in the BSRBR-RA.

Therefore, the BSRBR-RA proposes to open a new cohort of patients receiving these new targeted therapies, including the JAK inhibitors. Patients recruited to this cohort will be followed over the long-term to monitor the safety of these drugs. As the level of clinical use of these new drugs is presently unknown, we propose to set the recruitment target at 2000 patients per drug initially. We can then adjust this target as required based on prescribing practices and would seek additional approvals via further substantial amendments to the study at this time.

II. Increase in the size of the existing cohorts due to new drug licensing

As more and more of these bDMARDS are approved for use in the UK, the manufacturers are encouraged by the regulatory bodies (EMA, MHRA) to participate in the BSRBR-RA in order to capture long-term safety data. Therefore, we propose to extend the following two cohorts which have received prior approval from the ethics committee. Funding and resources are in place to accommodate these increases in cohort size.

a) IL-6 inhibitor Cohort

As part of amendment SA13 (approved 04/08/2010), we received approval to recruit a cohort of patients receiving the IL-6 inhibitor Tocilizumab. Now more IL-6 inhibitors are becoming available for the treatment of RA in the UK (currently Kevzara in 2017) and therefore we would like to extend this cohort to include 4000 patients.

b) Biosimilar Cohort

As part of amendment SA20 (approved 16/03/2015), we received approval to recruit a cohort of 2000 biosimilar patients. At the time, only two biosimilar drugs were available for use in the UK. Now there are 4 drugs in use which will increase to a total of 7 biosimilars available in 2018. In order to accommodate these new drugs, we propose to increase the sample size for this cohort to 6000 patients.

III. Outreach study invitation letter aimed at patients being re-registered

The BSRBR-RA has an invitation letter (BSRBR-RA Outreach Consent Invitation Letter, v1: 12/07/2016) to be used when potential participants are not due to be seen in clinic before the end of the 6 month recruitment window (each participant must be recruited within 6 months of beginning therapy with an eligible treatment). This Outreach invitation letter gives the participant the option of signing the consent form (following a telephone call from a member of the hospital's rheumatology/research team to explain the study and discuss any questions the patient might have) and returning it to the hospital to be signed by the health care professional.

Following feedback from participating centres we have identified the need for an additional outreach study invitation letter. This new Outreach invitation letter is more suitably worded to allow sites to re-consent those patients who are already part of the study, but are being re-registered because they switch to a new drug which is one of our actively recruiting cohorts. We re-consent patients at this stage to re-start the three years of follow up directly with the participant and the current outreach study invitation letter is more aimed at those patients who are joining the study for the first time. Therefore we have developed a new patient letter to be used in these circumstances, named 'BSRBR-RA Outreach Re-consent Covering Letter (Switchers) v1 – 17/07/2017.'

IV. Revisions to BSRBR-RA study documents

The following study documents have been updated to reflect the changes proposed above and generally improve consistency between the information we ask for on our data collection forms. They also involve changes incorporated following feedback from both participants and clinicians. Full details below.

BSRBR-RA Participant Information Sheet v9.0_17/07/2017
• Amended 'rheumatic conditions' to 'rheumatoid arthritis' in project title.
• Addition of wording around participant follow-up if they switch therapies and are re-registered.
• References to biologics amended to reflect addition of other targeted therapies.
• Updated examples of biologic and other targeted therapies involved in the BSRBR-RA while retaining reference to website for complete list of drugs the study is interested in.
• Removal of 'The BSRBR-RA will be most valuable if few people withdraw from it…' wording.
• Following feedback from participating centres the site contact section has been amended to be a bit more general and give sites the flexibility to put the details of whoever is co-ordinating the study at site level, which is often a research nurse rather than the consultant themselves.

BSRBR-RA Consent Form v9.0_17/07/2017
• Changed reference to Participant Information Sheet to reflect new version number/date.
• Amended 'rheumatic conditions' to 'rheumatoid arthritis' in project title.

BSRBR-RA Outreach Consent Invitation Letter v1.1 17/07/2017
• Title added.
• Section for sites to add hospital number added.

• References to biologics amended to reflect addition of other advanced therapies.
• References to HAQ/EQ5-D added.
• 'Contact' paragraph rephrased to better reflect most sites' preference.

BSRBR-RA Clinical Baseline Form v 11.2 17/07/2017
• References to biologics amended to reflect addition of other targeted therapies.
• Added 'Flixabi' to drug list and reference to BSRBR-RA website for most up to date list of eligible therapies.
• Re-addition of batch number collection.
• Re-wording of low disease activity collection section for those patients switching from an originator to a biosimilar of the same product to keep consistent with other BSRBR-RA forms and avoid potential confusion around when we can accept an indication of low disease activity in lieu of a DAAS-28 score.
• 'Chronic Bronchitis/emphysema' amended to 'Chronic Bronchitis/emphysema (COPD)' to maintain consistency with other BSRBR-RA forms.

BSRBR-RA Short Baseline Form v3.1_17/07/2017
• References to biologics amended to reflect addition of other targeted therapies.
• Added 'Flixabi' to drug list.
• Re-added batch number collection, including box to indicate if batch number is unknown.
• Added collection of reason for switch for those patients switching to a new biosimilar as this information is often missed at the follow up stage.
• Re-wording of low disease activity collection section for those patients switching from an originator to a biosimilar of the same product to keep consistent with other BSRBR-RA forms and avoid potential confusion around when we can accept an indication of low disease activity in lieu of a DAAS-28 score.
• 'COPD' amended to 'Chronic Bronchitis/emphysema (COPD)' to maintain consistency with other BSRBR-RA forms.
• Year of onset added to co-morbidity data collection to maintain consistency with other BSRBR-RA forms.
• Updated BSRBR-RA web address.

BSRBR-RA Clinical Follow-Up Form v11.3_17/07/2017
• References to biologics amended to reflect addition of other targeted therapies.
• Added reference to BSRBR-RA website for most up to date list of eligible therapies in re-registration section of page 1.
• Added 'Rituximab biosimilars' to 'Mabthera re-treatment' section.
• Removed drug list from 'infusions received' section on page 1.
• Added 'if available' to data collection for biologic/targeted therapy batch number.
• Updated BSRBR-RA website address.

BSRBR-RA Patient Baseline Questionnaire v5.0_17/07/2017
• Added 'other' option to title question.
• Addition of contact address to front page.
• Rephrased wording from 'Home telephone number' to 'Contact Phone Number.'
• Addition of email address to contact info collected and description of how this will be used by the BSRBR-RA.
• Added reference to CHI/HCN number.
• Work Disability Baseline questionnaire incorporated (Work Disability Questionnaire v1 04/03/2011 will no longer be in use as a standalone questionnaire).
• Removed question relating to PUVA therapy for patients with a diagnosis of Psoriatic Arthritis (As we no longer recruit these patients onto the study).
• Removal of question asking for town of birth.
• Removal of data collection relating to close friend/relative contact details in event of patient becoming lost to follow up.
• Removal of section referencing 'change of address postcard' as no longer used. Added wording around how patient should notify us if they have a change of address.
• Added question relating to e-cigarette/other nicotine/tobacco product use following patient feedback requesting more options regarding 'smoking status' data collection.
• Removal of SF36 section from document as no longer used by the study team.

BSRBR-RA Patient 6 Monthly Follow-up Questionnaire v7.0_17/07/2017
• Added question relating to e-cigarette/other nicotine/tobacco product use following patient feedback requesting more options regarding 'smoking status' data collection.
• Addition of contact address to front page and amended contact details at end of form.
• Work Disability Baseline questionnaire incorporated (BSRBR Work Disability Follow-up Questionnaire v1 04/03/2011 will no longer be in use as a standalone questionnaire).
• Removal of SF36 section from document as no longer used by the study team.

BSRBR-RA Poster for Patient Recruitment v2.0_17/07/2017

• References to biologics amended to reflect addition of other new therapies.
• Poster re-worded to be more patient friendly and remove specific references to eligibility criteria, replacing with more general information about the study and its aims, and what participation in the study involves, with an invitation to the patient to consult their rheumatologist at their next clinic appointment to see if they are eligible.
• Graphics updated to make the poster more consistent with the new BSRBR-RA website (www.bsrbr.org) and make it more visually appealing to potential participants.
• Updated web address and QR code.

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 Outreach Re-consent Covering Letter (Switchers)	1	17/07/2017
BSRBR-RA Participant Information Sheet	9	17/07/2017
BSRBR-RA Consent Form	9	17/07/2017
BSRBR-RA Outreach Consent Invitation Letter	1.1	17/07/2017
BSRBR-RA Clinical Baseline Form	11.2	17/07/2017
BSRBR-RA Short Baseline Form	3.1	17/07/2017
BSRBR-RA Clinical Follow-Up Form	11.3	17/07/2017
BSRBR-RA Patient Baseline Questionnaire	5	17/07/2017
BSRBR-RA Patient 6 Monthly Follow-up Questionnaire	7	17/07/2017
BSRBR-RA Poster for Patient Recruitment	2	17/07/2017

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:....03/08/2017.....

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 01/08/2017 16:51.

Job Title/Post:	Faculty Research Practice Governance Coordinator
Organisation:	University of Manchester
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