STUDY PROTOCOL

British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA)

Short Title: Toxicity from Biologic Therapy

Long Title: Prospective Observational Study of the Long-Term Hazards of Anti-TNF Therapy in Rheumatoid Arthritis

Professor Kimme Hyrich

Biologic Studies Group
Centre for Musculoskeletal Research, University of Manchester, UK

Version 2: 05/12/2018

IRAS ID: 64202

TABLE OF CONTENTS

ABBREVIATIONS

ACR	American College of Rheumatology
ADA	Anti-drug Antibody
ADR	Adverse Drug Reaction
AE	Adverse Event
BMQ	Beliefs about Medicines Questionnaire
BSRBR-RA	British Society for Rheumatology Biologics Register for Rheumatoid Arthritis
Brief-IPQ	Brief Illness Perception Questionnaire
BSR	British Society for Rheumatology
CHI	Community Health Index
CI	Confidence Interval
CQR	Compliance Questionnaire Rheumatology
CVA	Cerebrovascular Accident
DAS	Disease Activity Score
DMARD	Disease-modifying Anti-rheumatic Drugs
DMEC	Data Monitoring and Ethics Committee
EMA	European Medicines Agency
ENCePP	European Network of Centres for Pharmacoepidemiology and Pharmacovigilance
EQ-5D	EuroQol 5D Questionnaire
ESQ	Event Specific Questions
GPP	Good Pharmacoepidemiology Practices
GVP	Good Pharmacovigilance Practices
HAQ	Health Assessment Questionnaire
HCN	Health and Care Number
HL	Hodgkin's Lymphoma
IR	Incidence Rate
ISPE	International Society for Pharmacoepidemiology
JIA	Juvenile Idiopathic Arthritis
MAA	Marketing Authorisation Application
MARS-5	Medication Adherence Report Scale
MedDRA	Medical Dictionary for Regulatory Activities
mAb	Monoclonal Antibody
MI	Myocardial Infarction
MS	Multiple Sclerosis
MTX	Methotrexate
NHL	Non-Hodgkin's Lymphoma
NHS	National Health Service
NICE	National Institute for Health and Clinical Excellence
NSAID	Non-Steroidal Anti-Inflammatory Drug
PML	Progressive Multifocal Leukoencephalopathy
PT	Preferred Term
PY	Person-Years
RA	Rheumatoid Arthritis
SAE	Serious Adverse Event
sc	Subcutaneous
SOP	Standard Operating Procedure
TB	Tuberculosis
TNF	Tumour Necrosis Factor
UK	United Kingdom

PROTOCOL SUMMARY

BSRBR-RA Protocol	
Sponsor	The University of Manchester
Chief Investigator	Professor Kimme Hyrich
Title of the study	Prospective Observational Study of the Long-Term Hazards of Anti-TNF Therapy in Rheumatoid Arthritis
Short title	Toxicity from Biologic Therapy
Country	UK
Study Design	Prospective observational cohort study, non- interventional
Objectives	1. To establish cohorts of patients starting any new biologic, biosimilar or other new targeted therapy for rheumatoid arthritis (RA). 2. To compare the risk of key safety outcomes between UK patients with RA starting any new biologic, biosimilar or other new targeted therapy with appropriate comparator cohorts already established in the BSRBR-RA.
Endpoints	The BSRBR-RA is able to evaluate a range of serious safety outcomes associated with therapies used to treat RA including but not limited to death, malignancies, cardiovascular disease and serious infections.
Methodology	This is a non-interventional, observational study, in which all patients starting treatment with targeted therapies are enrolled for observational follow-up. The BSRBR-RA has studied the long-term effectiveness and safety of biological treatments prescribed at NHS hospitals in the UK since 2001 when the study first started. Data are captured via the hospitals, via the patients directly and by linkage with national outcome databases.

BACKGROUND

Rationale for establishing the BSRBR-RA

The British Society for Rheumatology Biologics Register for Rheumatoid Arthritis (BSRBR-RA) was established in 2001 to study the safety of biologic therapies in patients with rheumatoid arthritis (RA). For the first 7-8 years the main focus was on the study of the safety profile of the first three TNF-inhibitor (TNFi) agents (Humira, Enbrel and Remicade) as a class and as individual therapies. With the exception of the risk of developing tuberculosis, BSRBR-RA has not demonstrated any clear differences in adverse event profile between these agents. At the time, the most appropriate comparison group for these three TNFi agents was patients with active RA receiving treatment with conventional synthetic disease modifying anti-rheumatic drugs (csDMARDs).

A number of new biologic, biosimilar and other targeted therapies have since been developed and are receiving National Institute for Health and Clinical Excellence (NICE) approval. Some of these drugs are being used after TNFi therapy and some are proposed for first-line use following csDMARD failure. These agents are all targeted therapies and act on cells, cytokines or other pathways which play a key role in inflammation and the functioning of the immune system. With each new agent there has to be concern as to what the safety profile may be in routine clinical use. Clinical trials of new agents exclude many groups of patients at higher risk of infection, for example those with co-morbidities such as uncontrolled diabetes and also those with other co-morbidities such as renal impairment or coronary heart disease. In routine practice the occurrence of serious adverse events may be higher than in clinical trials.

Need for a comparison cohort

There is an increased risk of premature mortality, serious infection, cardiovascular disease and lymphoproliferative malignancy in patients with RA and other connective tissue diseases, independent of the treatment they have received. Thus the patients most likely to receive these new therapies are already at increased risk of adverse outcomes. It is therefore fundamentally important not just to document the occurrence of these events in a treated cohort of patients but to compare their occurrence with that which might have occurred if such patients had remained on “conventional” therapy or received a different biologic, biosimilar or other targeted therapy. Whereas originally the most appropriate comparison group was those patients on csDMARDs who were biologic naïve, these patients are increasingly those at the milder end of the disease spectrum who have a lower background risk of all the serious adverse events of interest. Patients who do not respond to csDMARDs are now quickly moved onto biologic therapies. The closest we can now get to patients with the same background risk of, for example infection and malignancy, as those patients being treated with the new biologic agents, is a comparison cohort of patients with similar disease severity being started on their first TNFi agent. As more therapies are approved for use in the UK, the appropriate comparison cohort

may change over time and the BSRBR-RA will be in a position to select the most appropriate comparison to the therapy in question.

Balancing effectiveness and safety

Careful observation of large cohorts of patients is needed to detect any statistically significant increase in risk either of malignancy or infection. If an increased risk were found, then this should be balanced against the benefits in terms of improvement of quality of life. Furthermore, it is important that surveillance also examines the occurrence of other co-morbidities and mortality. It is possible that long-term effective disease suppression might actually reduce all-cause mortality and lymphoproliferative malignancy, for example.

It therefore follows that for all new biologic, biosimilar and other targeted therapies there is a need for an epidemiologically rigorous surveillance programme, which would evaluate any excess risk in the occurrence of such serious adverse events after allowing for confounding factors particularly of disease severity and other concomitant therapy. Long term morbidity and mortality and the effects of these therapies will be assessed over time to evaluate the relative risk. Thus, follow-up of study participants will remain ongoing whilst the study has approvals in place (some participants have been in the study for up to 15 years so far).

Objectives

Hypotheses to be tested

Primary: That any new biologic, biosimilar or other new advanced targeted therapy in patients with RA is associated with a similar risk of developing serious infections compared to patients with similar disease activity receiving either established TNFi therapies or csDMARD therapy.

Secondary: That any new biologic, biosimilar or other new advanced targeted therapy in patients with RA is associated with a similar risk of developing malignancy and other specified outcomes (such as myocardial infarction) compared to patients with similar disease activity receiving established TNFi therapies or csDMARD therapy.

In developing the methods for a study to test these hypotheses it is assumed that any increased risk would become apparent within 5 years of starting therapy.

Primary objectives

1. To establish cohorts of patients in the UK starting any new biologic, biosimilar or other new targeted therapy for rheumatoid arthritis (RA).
2. To compare the risk of key safety outcomes between patients with RA starting any new biologic, biosimilar or other new targeted therapy with appropriate comparison cohorts including those starting an established TNFi or those with active disease on csDMARD therapy.

Endpoints of interest/outcome measures

The occurrence of and risks associated with any new biologic, biosimilar or other new targeted therapy fora range of endpoints, including but not limited to the following, will be evaluated:

1 Serious Infection
2 Tuberculosis
3 Progressive Multifocal Leukoencephalopathy (PML)
4 Myocardial Infarction/ Serious Acute Coronary Syndrome
5 Cerebrovascular Accident (CVA)
6 Serious Congestive Heart Failure
7 Malignancy, Inc. Skin Cancer/Bowen's Disease
8 Lymphoproliferative Malignancy
9 Serious Hepatic Dysfunction/ Failure
10 Serious Lower Gastrointestinal Ulcer/ Bleed/ Perforation
11 Hepatitis B Reactivation
12 Serious Lupus/ Lupus-Like Illness
13 Serious Skin Reaction
14 Demyelination, Optic Neuritis
15 Serious Hypersensitivity Reaction
16 Aplastic Anaemia, Pancytopaenia, Serious Neutropenia
17 Serious Haemorrhage
18 Serious Pulmonary Embolism/Deep vein thrombosis
19 Pregnancy
20 All-cause mortality

Subsidiary hypotheses

The following subsidiary hypotheses will be tested:

(i) Any increased or decreased risk for any of the above endpoints is related to duration of therapy.

(ii) There are identifiable disease characteristics that act synergistically to alter risk.

(iii) Previous or concomitant therapy with biological or multiple immunosuppressive agents act synergistically to alter risk.

Study Design/Methodology

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. Data capture and follow-up are the same for all cohorts within the BSRBR-RA.

The British Society for Rheumatology (BSR) treatment guidelines recommend that all patients receiving biologic, biosimilar and other new targeted therapies for RA, should be registered with the BSRBR-RA.

It is recognised that study recruitment may be affected by external factors in the UK such as:

1. NICE technology assessment.
2. Funding by NHS/trusts.
3. Uptake by prescribing rheumatologists.
4. Local issues at sites including resources.

Study Enrolment and withdrawal

On commencing a therapy currently under recruitment by the BSRBR-RA, the rheumatology/research team will ask the patient if they would like to participate in this observational study. If they consent to participate, the rheumatology/research team will complete and submit the baseline documentation to the BSRBR-RA team at the University of Manchester who will register the patient in the study. Patients are not obligated to participate and participation is not related to the choice of therapy, decision to treat or access to the treatment.

Informed consent will be obtained by the appropriate personnel who are authorised to do so by the local principal investigator.

Patients can also be recruited to the BSRBR-RA via an outreach consent method. This gives participating sites the option of sending the patient information sheet, transparency information sheet and consent form (alongside patient completed questionnaires including the

Health Assessment Questionnaire (HAQ) and the Euro-QOL (EQ)-5D) to any patients identified as eligible, alongside a telephone call to discuss the study and give potential participants the opportunity to ask any questions. The forms can then be completed by the patient and returned to the site to be countersigned. The completed forms would then be submitted to the BSRBR-RA team at the University of Manchester who will register the participant in the study.

Potential participants are asked to discuss any concerns they might have with their rheumatology team or the BSRBR-RA team in the first instance.

Participants are free to withdraw at any time from the study after giving signed consent, by contacting the BSRBR-RA staff (by phone, letter or email). Participants can then discuss the desired level of withdrawal from the following three options:

> Option 1: No further participant contact:
> BSRBR-RA would not send participants any further questionnaires or surveys about their health, but would continue to receive information from their rheumatology team at the hospital and via the linkage with the national outcome databases.
>
> Option 2: No further participant or hospital contact:
> BSRBR-RA would not send participants, or the rheumatology team at the hospital, any further forms or surveys asking about the participant's health. The participant's record would still be linked with the national outcome databases.
>
> Option 3: Complete withdrawal:
> BSRBR-RA would not send out any surveys or forms to participants or their rheumatology team at the hospital. The study team would also contact the national databases to un-link a participant's record so no further information was received via the national outcome databases from the time of withdrawal.

If a participant withdraws from the study, all data collected by the study to the point of withdrawal will be retained.

Exposed Cohort

For each new biologic, biosimilar or other new advanced therapy drug the exposed cohort will be patients under the care of a consultant rheumatologist with rheumatoid arthritis newly starting therapy with that biologic, biosimilar or other new advanced therapy.

Some patients will already be enrolled in the BSRBR-RA on other drugs and then switch to one of the newly recruiting targeted therapy cohorts. Key clinical data (drug therapy, disease activity, zoster vaccine, tuberculosis (TB) screening, new comorbidities; http://bsrbr.org/hospitals/data-collection/registration/) will be requested at time of switch.

External validity will be maximised by attempting to ascertain all patients, newly treated with that biologic, biosimilar or other new advanced therapy agent. The support of the BSR, with help from the pharmaceutical industry, will be necessary to ensure maximal recruitment.

Recruitment will be co-ordinated at a national level. The study will be based in England, Wales, Scotland and Northern Ireland. Historically, patients without a diagnosis of RA (such as psoriatic arthritis, ankylosing spondylitis and other rheumatic conditions) were recruited to the study, but this has since been limited to RA only. Follow-up of these historic non-RA patients continues as per the process outlined in this protocol.

Due to the nature of the study, new cohorts open as new treatments are launched to market. A full up-to-date list of eligible treatments can be found here:

http://bsrbr.org/hospitals/eligibility/

Comparator Cohorts

Comparator Cohort 1
The first comparator cohort will be patients recruited to the BSRBR-RA with RA who have been registered within 6 months of first exposure to an established TNFi drug (e.g. Humira, Enbrel or Remicade). For analyses, patients who switch to a second biologic or other targeted therapy will have their follow-up censored at the time of switching treatments. They will then be eligible to enter an 'exposed' cohort if they go on to be treated with one of these new targeted drugs under recruitment.

Comparator Cohort 2
The second comparator cohort will be a historical RA cohort of patients treated with csDMARDs recruited to the BSRBR-RA from a select number of sites within the UK (recruited between 2002 and 2008). Patients who subsequently progress to a biologic, biosimilar or other new targeted therapy will, for the purpose of analysis (see below), have their follow-up censored at the time of the first dose, thus they will contribute patient months of follow-up prior and up to the treatment change date. They will then be eligible to enter an 'exposed' cohort but only if the subject consents to being re-registered as an "exposed patient".

In addition, as more therapies are approved for use in the UK and join the BSRBR-RA, it is feasible that appropriate comparison cohorts may change over time.

Comparability between cohorts

The greatest concern with a study of this design is the potential lack of comparability between the exposed cohorts and the comparison cohorts in relation to their underlying risk of endpoint development. If there is an important imbalance between key confounders between the groups then this could reduce the likelihood of obtaining robust estimates of risk.

The key confounders to be measured at baseline include details of disease severity, including symptom duration, current Health Assessment Questionnaire (HAQ), current significant comorbidities and all relevant previous therapies. In order to control for confounding effects due to the disease status, the historical csDMARDs cohort was required to have baseline DAS28 ≥ 4.2 despite the current treatment of at least one csDMARD.

Since the latest targeted therapies are a new generation of biologic DMARDs, patients who are prescribed these drugs may include patients who probably had failed TNFi or csDMARDs, and thus are more likely to be those who had more severe disease, longer disease duration, and more comorbidities than the comparison groups. Therefore, the BSRBR-RA also has the option to select from within exposed cohorts, subsets of patients for analysis who can form a more appropriate comparison cohort depending on the research question.

It is very important to control for the related confounding during analyses in addition to the inclusion criteria. For this reason, after applying all the inclusion criteria, statistical adjustment, especially using propensity scoring techniques, will be adopted to control for the potential residual confounding. Stratified analysis or subgroup analysis will also be considered for major confounding factors if deemed appropriate after descriptive analysis. Furthermore, sensitivity analysis will be conducted to evaluate the impact of disease severity, duration, and medical treatment history on the results for any residual confounding that may remain after application of inclusion/exclusion and statistical adjustment in the modelling, and to better understand the impact of analytical decisions on the results.

Analyses undertaken to date comparing the established TNFi cohorts with the csDMARD group have not revealed any serious imbalance that cannot be adjusted for in subsequent analyses.

Inclusion criteria

(i) Patients with rheumatoid arthritis with a diagnosis of RA by a consultant rheumatologist and be within 6 months of first exposure to biologic, biosimilar or other new advanced therapy drug.
(ii) Minimum of one treatment with a biologic, biosimilar or other new advanced therapy agent.
(iii) Age 16 years or older (no upper age limit).
(iv) Willingness to give informed consent for long term follow-up.
(v) Evidence of a personally signed and dated informed consent indicating that the patient (or legally acceptable representative) has been informed of all important aspects of the study, a copy of which will be held in the patient's medical records at the hospital.
(vi) The csDMARDs cohort is required to have active RA at recruitment with active disease (guide DAS28 ≥ 4.2) in spite of current treatment with at least one csDMARD in order to control for confounding due to disease severity.

Exclusion criteria

There are no exclusion criteria for this observational study.

Data collection

The following link shows the data collected in the study which is also summarized below:
http://bsrbr.org/hospitals/data-collection/

Baseline Data

The following information will be collected by the recruiting clinician/nurse, using a standardised form:

(i) NHS/CHI/HCN number (National Health Service identification number).
(ii) Diagnosis (including the presence or absence of those features listed in ACR criteria for RA).
(iii) Date of birth, gender, year of recalled symptom onset.
(iv) Previous drug history of csDMARDs and biologics, biosimilar or other new advanced therapy, including duration of therapy.
(v) Significant co-morbidity.
(vi) All current therapy.
(vii) Joint replacements/surgery (total knee replacement, total hip replacement, etc.).
(viii) Tuberculosis screening.
(ix) DAS28 (disease activity score).
(x) Health assessment questionnaire (HAQ) and EuroQol – 5 Dimensions (EQ-5D) questionnaire
(xi) Height, weight, blood pressure.

In addition, some personal and medical information will be obtained directly from each patient recruited (smoking history (current, former, or never), occupation, working status (full time, part time, unemployed, unable to work, or retired), alcohol consumption, and race).

No biological samples are collected and/or stored. Therefore biomarker, drug levels and anti-drug antibodies are not available.

For re-registering/switching patients on biologic, biosimilar or other new targeted therapy who are already participating in the BSRBR-RA, there is a simplified baseline information form which captures a subset of the above data most likely to change over time.

Follow-up Data

The follow-up of all study participants will be co-ordinated by the BSRBR-RA team at the University of Manchester and will include:

- RA treatment changes including biologic, biosimilar and other targeted therapies received in the previous observation period*.
- Development of any serious adverse event including but not limited to the adverse events of interest.
- Non-serious adverse events.
- DAS28.

*Once the BSRBR-RA web system has been launched a list of current drugs at follow up will be maintained.

Follow-up Schedule

Follow-up will be organized via the (1) hospital, (2) the patient directly and (3) by linkage with national databases for major health outcomes.

Hospital/clinical follow-up

The healthcare team at the hospital will be contacted every 6 months for the first 3 years and then annually thereafter and asked to complete a standard data form covering any change in treatment over the preceding 6 months/year. This includes continuation on drug and dates and reasons for stopping, with details of any change in dose and commencement of any new co-therapy. Clinical information to permit calculation of the DAS28 will also be collected. Additional data will also be requested for all new serious co-morbidities and serious adverse events (SAEs) occurring in the previous period. Event Specific Questions (ESQs) will be captured for the SAE endpoints of particular interest (listed on page 6).

Other items may be added to this list from time to time as new therapies join the study and the current list is available on the BSRBR-RA website (http://bsrbr.org/hospitals/data-collection/adverse-events/).

Follow up continues for the duration of the study and where appropriate approvals are in place.

Each hospital will have their own local arrangements for completing the forms.

Once the data has been sent to the BSRBR-RA offices, all SAEs are processed by the study team according to BSRBR-RA pharmacovigilance procedures.

The DAS28 will be collected to correspond, as closely as routine clinical practice allows, with the scheduled follow-up dates. This will allow a capture of treatment effectiveness at 6 and 12 months following start of therapy during routine clinical practice, to be included in a study of predictors of treatment response (e.g. prior anti-rheumatic treatment, disease and demographic factors).

Participant Follow-up

Study participants will also be contacted every 6 months for the first three years and asked to complete a patient diary which includes data about hospital admissions, new hospital referrals and details of any new drugs prescribed and the condition being treated. They will be asked to complete a series of questionnaires at these time points including the following:

a. HAQ
b. EQ-5D
c. Work Productivity Survey
d. 'Views on illness, treatment and general health' booklet (containing Brief-IPQ, MARS-5, CQR and BMQ questionnaires designed to measure treatment adherence. Collected only at baseline, 6 and 12 month follow up points).

Following the report of any serious morbidity, either by participant or healthcare professional, the referring doctor will be contacted by the BSRBR-RA and asked to provide further details, where available. For specific morbidities of interest certain specific details will be requested. All serious morbidities will be coded by a trained nurse using the MedDRA system, a licensed copy of which is obtained annually.

Data collection methods

Initial follow-ups of both patients and their health care team at the hospital will be returned by post. A web-based data collection system is under development to allow the clinical team to submit baseline and follow up data directly. The web system will be launched as soon as development, testing and a pilot phase has concluded. Attempts will be made to follow-up non-responders. Non-responders to one follow up will nonetheless (unless further follow up is refused) be contacted again at the next follow up point.

Follow-up via linkage with national databases

All exposed and comparison individuals will be "flagged" with the national death and cancer registers for continuous surveillance and notification of mortality and the development of any malignancy. Death certificate details will be obtained for those who die and details of type and site of cancer for those who develop a malignancy will be provided. Where appropriate approvals are in place, linkage to other national database such as Hospital Episodes Statistics may be undertaken to enrich the study data further.

Re-registration in the study

Should a BSRBR-RA participant switch to a different biologic drug/ advanced targeted therapy than the one for which they were registered at the start of the study, we would seek to re-

register the patient under a new BSRBR-RA study ID, provided the patient is happy to be re-registered and give new informed consent.

A patient will not be eligible for re-consent should they be recommencing a biologic, biosimilar or other targeted therapy with which they have already been treated.

In the event of switching, the clinical team will need to fill a short baseline form and a HAQ and EQ-5D for the new drug and send to the study offices alongside the new consent form for re-registration. They will then be assigned a new ID number and the follow up period will start again.

Sample Size

The sample studied needs to be large enough and the subjects followed for a sufficient period, to detect an increase in the incidence of the key adverse events considered of interest.

The sample size calculation will be based on the comparison of the new treatment group with the reference groups. It will be based on person-time and assume a minimum of 5 person years of follow up per subject recruited. An initially non-exposed (to the new treatment) subject who, during follow up, commences therapy with a different biologic or targeted therapy, then becomes censored for the purposes of analysis. Their subsequent disease experience may count towards the exposed person-years at risk for some analyses. Loss to follow up, including death from an unrelated cause, will also reduce the available person years. The sample studied needs to be large enough and the subjects followed for a sufficient period, to detect an increase in the incidence of those key adverse events considered of interest.

Mortality and the occurrence of cancer will to be followed via the national cancer and death registers in England, Wales, Scotland and Northern Ireland.

There inevitably will be a large number of subjects exposed to multiple agents, which renders sample size calculations difficult. This problem will need to be adjusted for in the analysis and allowance made for possible interactive effects. Interactions can be difficult to detect and require large sample sizes. It thus seems prudent to ensure the sample sizes chosen are the minimum target recruitment.

Data Analysis

All statistical analyses will be performed using the most recent version of STATA. The initial analyses will consist of comparisons in baseline status between the individuals in the different cohorts. The final analysis of endpoints will be based on comparing the risks of events over time using Cox-proportional hazards regression, taking into account differences between groups as potential confounders and effect modifiers.

Interim analyses will be undertaken at 6 monthly intervals and include recruitment details, baseline characteristics and crude event rates. These reports are produced twice a year (January and July) and shared with the pharmaceutical companies participating in the BSRBR-RA. Monthly recruitment reports will also be generated. Such analyses will be a guide to the ultimate levels of recruitment and length of follow-up required. Decisions as to the timing of publications and the need for continued follow-up and/or recruitment can only be taken in light of results from such analyses.

A Data Monitoring and Ethics Committee (DMEC) has been established by the British Society for Rheumatology (BSR), analogous to a Data Safety and Monitoring Board established for major clinical trials. The DMEC is independent of the Chief Investigator and also of any of the pharmaceutical companies involved, and has the power to request interim analyses and advise on the timing and nature of any publications. The DMEC includes at least one epidemiologist and one statistician.

Quality Control

All information received on serious adverse events (SAEs) will be reviewed by one of two trained registered nurses prior to coding. Reports can arise from the hospital team, patients or the national registers. In order for SAEs to be included in analysis, the following information is required:

(i) A legible and recognized disorder/signs and symptoms
(ii) The date of the event
(iii) Which biologic drug the patient was on at the time of the event

Where this information is missing, the BSRBR-RA pharmacovigilance team contacts the hospital to validate and confirm the details around the serious adverse event. Where a serious adverse event is patient reported, a request for information is always sent to the hospital for validation. Events that do not fall under the definition of an SAE are not subject to such additional validation. The data undergoes regular validation checks both manually and automatically.

Limitations of the Research Methods

Despite the strengths of this observational study, data must be evaluated in light of their limitations. For example, consistent with most observational studies, the possibility of channelling biases, endpoint misclassification, and generalizability are of concern when evaluating event rates.

Event misclassification is of particular concern within the observational setting due to less stringent monitoring relative to clinical trials. While the BSRBR-RA has an established system to identify and capture endpoint data, it is not feasible in such an observational study to verify all events via source documentation.

Protection of Study Participants

All parties will ensure protection of the study participants' personal data and will not include patient names or other identifiable data on any reports, publications or in any other disclosures, except where required by law. In case of data transfer, appropriate data sharing agreements will be put in place with approved third parties to maintain high standards of confidentiality and protection of personal data.

All participants in the BSRBR-RA have provided informed consent for participation in the study (Study Ethics Reference: 00/8/053).

Ethical Conduct of the Study

The study will be conducted in accordance with legal and regulatory requirements, as well as with scientific purpose and will follow accepted research practices described in Guidelines for Good Pharmacoepidemiology Practices (GPP) issued by the International Society for Pharmacoepidemiology (ISPE), European Medicines Agency (EMA), European Network of Centres for Pharmacoepidemiology and Pharmacovigilance (ENCePP) Guide on Methodological Standards in Pharmacoepidemiology.

Contact details

- **Email:** biologics.register@manchester.ac.uk
- Phone: 0161 275 1652/7390
- Fax: 0161 275 1640

- Website: http://bsrbr.org/hospitals/
- Social Media (Twitter): @BSRBR_RA