NHS
National Patient Safety Agency

National Research Ethics Service

NOTICE OF SUBSTANTIAL AMENDMENT

For use in the case of all research other than clinical trials of investigational medicinal products (CTIMPs). For substantial amendments to CTIMPs, please use the EU-approved notice of amendment form (Annex 2 to ENTR/CT1) at http://eudract.emea.eu.int/document.html#guidance.

To be completed in typescript by the Chief Investigator in language comprehensible to a lay person and submitted to the Research Ethics Committee that gave a favourable opinion of the research ("the main REC"). In the case of multi-site studies, there is no need to send copies to other RECs unless specifically required by the main REC.

Further guidance is available at http://www.nres.npsa.nhs.uk/applicants/review/after/amendments.htm.

Details of Chief Investigator:	
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Full title of study:	Prospective Observational Study of the long term hazards of anti-TNF therapy in rheumatoid arthritis
Name of main REC:	North West 5 REC – Haydock Park
REC reference number:	MREC 00/8/53
Date study commenced:	October 2001
Protocol reference *(if applicable)*, current version and date:	Protocol dated 06/10/2003
Amendment number and date:	Today's date: 12 July 2010

Type of amendment (indicate all that apply in bold)

(a) Amendment to information previously given on the NRES Application Form

Yes *No*

If yes, please refer to relevant sections of the REC application 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 to the REC and given an unfavourable opinion?

Yes ***No***

Summary of changes

Briefly summarise the main changes proposed in this amendment using language comprehensible to a lay person. Explain the purpose of the changes and their significance for the study. In the case of a modified amendment, highlight the modifications that have been made.

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 two separate areas (i) proposed electronic data collection in the BSRBR, and (ii) change to patient information sheet and consent form to reflect name changes in governmental departments.

Electronic Data Collection

The BSR Biologics Register currently collects data from clinicians across the UK using paper-based questionnaires that are entered onto a Microsoft Access 2003 database by a team of Project Assistants at the Biologic Studies Group offices. A move towards electronic data collection is vital for the ongoing success of the

Register. It is also important for the future of the Register to keep up with contemporary data collection methods. Frequent input and feedback from end-users will be vital to the success of this system. It is hoped that the comparative ease of the new system would encourage the clinicians and research nurses to submit data to the Register in a more efficient way as well as reducing the scope for data entry error, as the information is entered directly at source in the hospital rather than by a separate data-entry team.

Moving to a web-based system will be a staged process and we propose to test the first phase of the new system over the coming months at eight pilot centres across the UK, before extending this system to all centres and finally all of the clinician-completed data collection forms. The data collection forms remain the same as they currently are, and the web based system will not be used to collect information from the patient directly. The serious infection 'Event of Special Interest' (ESI) form will be the first form used in the pilot study; this is a single page verification questionnaire that is sent out to clinicians asking for more details regarding specific serious adverse events, i.e. in this case serious infections. When the BSRBR team are informed by a clinician at a designated pilot centre that one of their patients has experienced a serious infection, they will be asked to login and complete the ESI form online and submit it to the BSRBR database. Training by the BSRBR team in using the new system will be provided to ensure a smooth transition. By testing a single page data collection form in the pilot study, any problems should be identified easily before the system is extended to further BSRBR data collection forms.

The pilot phase
The pilot database has been developed using the latest version of SQL server that the University of Manchester provides (currently SQL server 2005). Encryption of the data is performed using standard tools in Microsoft.NET, which ensures that the data is unreadable to any person that does not have a password and is not registered as a user. A password to use the system is granted only by requesting access from the BSRBR Team via the BSRBR website. In the first instance, only clinicians and other members of the research team at the designated pilot centres will be able to request access but this will be expanded to include all centres once the pilot study is complete.

When viewing the BSRBR web page:

http://www.medicine.manchester.ac.uk/musculoskeletal/research/arc/clinicalepidemiology/pharmacoepidemiology/bsrbr/

there will be an option for the pilot centres to register as a new user on the site. Here, the clinician/nurse will enter their name, job title, department, hospital details where they work and their telephone number. They are then prompted to choose their own username and password, provide a contact email address and create a security question that is used if the password is forgotten. This information is entered into a 'customer table' in the database where it is flagged as information from a new user. All new users will be flagged as 'not verified' until the BSRBR team then verifies that the applicant works at the named hospital by a telephone call. The flag is then amended to indicate that the account has been verified and the user can now have access to the database. Each user will only be allowed to view their own patient's data.

The User ID and password that the clinician chooses is encrypted in the database using default Microsoft 128bit encryption. This means that members of the BSRBR study team will not be able to view the passwords. If the user forgets the password, they will be asked the security question provided in the registration process, and their password will be emailed to them.

As detailed above, each new user will be verified by the BSRBR before any encrypted information is transferred, ensuring that only approved individuals are able to use the system. The general public can access the BSRBR web page, but will have no access to the data-entry area of the website. 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. The BSRBR Team will be able to view all the information that has been entered by any centre.

System security
The database will be held on a secure server and will follow standard University of Manchester security policies. The data will be stored within an access-restricted data share on the University's network storage infrastructure, which is the recommended (by University IT Services) location for storing sensitive or critical University data.

The storage infrastructure is hosted across two data centres (approx 2km apart) for resilience and disaster recovery purposes. Physical access to the data centres is strictly limited to data centre staff and a limited number of authorised IT Services staff. The data centres are protected by physical and electronic access security systems, swipe card access in and out of the data centres and CCTV coverage. The data centres are locked down out of hours and access is only with the prior agreement of the data centre manager. The campus network perimeter arrangements ensure that transmitted data is not visible from off campus. Network segmentation restricts the visibility of transmitted data on campus. The University has a Network Policy of securing all network cabinet access and restricting access to authorised IT staff.

Change to Consent Forms and Participant Information Sheets

Minor wording changes have been made to the consent form and participant information sheet to incorporate the change in structure of the national NHS registers. The National Health Service Central Register (NHS CR), which was previously part of the General Register Office (GRO) are now separate organisations. Officially the NHS central register was transferred to the NHS-Information Centre in 2008:

(http://www.ons.gov.uk/about/who-we-are/our-services/medical-research/index.html).

Please refer to point three on the consent form and information sheet which have therefore been revised to reflect this governmental department change of name. Two further changes have been made (i) the University of Manchester is now the sponsor of the study and, (ii) the arc has changed it's name to Arthritis Research UK.

Any other relevant information

Applicants may indicate any specific ethical issues relating to the amendment, on which the opinion of the REC is sought.

List of enclosed documents

Document	*Version*	*Date*
Previously approved protocol	No version	06/10/2003
BSRBR Consent Form	7	23/07/2010
BSRBR Participant Information Sheet	7	23/07/2010

Declaration

- I confirm that the information in this form is accurate to the best of my knowledge and I take full responsibility for it.
- I consider that it would be reasonable for the proposed amendment to be implemented.

Signature of Chief Investigator: .....

Print name: KIMME HYRICH

Date of submission: 20.8.10