NHS
Central Office for Research Ethics Committees
(COREC)

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.corec.org.uk/applicants/apply/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 MREC
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 14/12/2006

Type of amendment (indicate all that apply in bold)

(a) Amendment to information previously given on the REC 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 <u>either</u> the revised protocol with a new version number and date, highlighting changes in bold, <u>or</u> 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.

Anti-TNFα therapies have proved effective in clinical trials for treating rheumatoid arthritis by controlling disease and suppressing disease activity. The BSR Biologics Register already monitors the long-term use of the anti-TNFα therapies (currently etanercept, infliximab, adalimumab and anakinra (an IL-1 receptor antagonist)) in these patients. However, there are a proportion of patients who will not respond to these drugs. The availability of other anti-TNFα agents such as the new anti-B cell therapy, rituximab (MabThera, Roche Products Ltd) represents a therapeutic alternative to patients for whom either anti-TNFα therapy may be contra-indicated or in whom it has been tried and failed.

Rituximab acts by depleting B lymphocytes which carries the CD20 'marker'. It was introduced in 1997 for the treatment of non-Hodgkin's lymphoma and over 700,000 patients have been treated for this indication.

It has recently been shown to be effective and well tolerated (in the short term) in patients with RA. There are few data in RA patients on longer term complications. Unlike with the anti-TNFα agents, lymphoma is unlikely to be a problem but there are a number of unanswered questions as to whether B-cell depletion will lead to a longer term risk of infection and other immune abnormalities. Of particular interest is the likelihood that many patients with RA treated with rituximab will have already been treated with anti-TNFα agents and that this prior treatment might influence there subsequent infection risk.

An extension to the BSRBR to recruit rituximab (MabThera)-treated patients provides an invaluable opportunity to assess the efficacy and comparative safety of this additional agent in clinical practice. Some patients already registered with BSRBR are likely to switch to rituximab if their current therapy is not effective but there will also be a group of patients who have not been registered with BSRBR in the past as they started etanercept after BSRBR had completed recruitment of etanercept patients (May 2005 onwards).

It is proposed that BSRBR recruit 1100 patients who are receiving rituximab over a three-year period (see protocol for sample size calculations (page 6)). Baseline data collection and follow-up will be the same as for the current anti-TNF therapy patients. Since these patients are likely to have tried and failed previous anti-TNF therapy, it is proposed that BSRBR collect further data on this previous exposure at registration (Prior Biologic Therapy Exposure Form). The patient information sheet and consent form will not change as the anti-TNF therapies are referred to as "new therapies". For patients who switch to rituximab from other biologic therapies, it is proposed that BSRBR collect disease measures and medication at time of the switch (Rituximab supplementary switch form)

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
New rituximab protocol	Version 1	01/09/2006
Consultant baseline questionnaire	Version 6	14/12/2006

Consultant follow-up questionnaire	Version 6	14/12/2006
Prior biologic therapy exposure form	Version 1	14/12/2006
Rituximab supplementary switch form	Version 1	14/12/2006

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: ……Professor Alan Silman…

Date of submission: ……..