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.

Biologic 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 and adalimumab), anakinra (an IL-1 receptor antagonist) and rituximab (an anti-B cell therapy) in these patients. However, there are a proportion of patients who will not respond to these drugs. The availability of other biologic agents such as the new IL-6 inhibitor tocilizumab (RoActemra, Roche Products Ltd) represents a therapeutic alternative to patients for whom either biologic therapy may be contra-indicated or in whom it has been tried and failed.

Tocilizumab is a monoclonal antibody that acts by inhibiting cytokine interleukin 6 (IL-6).

Reducing the activity of IL-6 may reduce inflammation in the joints, prevent long term damage and relieve certain systemic effects of rheumatoid arthritis (RA). In combination with methotrexate, tocilizumab is recommended by the National Institute for Health and Clinical Excellence (NICE) for the treatment of moderate to severe active RA in people who have not responded to previous biologic or DMARD therapy, but can be given as monotherapy in case of intolerance to methotrexate, or if continued treatment with methotrexate is not appropriate[1]. Tocilizumab is administered as an intravenous infusion given over an hour, and is given once every four weeks.

Cardiovascular mortality remains the leading cause of death in patients with RA. In the randomised controlled trials of tocilizumab, increases in fasting mean plasma lipid levels were observed in the tocilizumab-treated patients. These elevations were apparent from the time of first scheduled testing at week 6 and remained elevated during continued dosing, but without further increases. The frequency of coronary ischaemic events and stroke in clinical trials is low and there is no evidence that tocilizumab increase the risk of such events. However, in view of the observed increase of lipid levels, cardiovascular adverse events (myocardial infarction and stroke) are outcomes of interest, especially for longer-term follow-up in patients receiving tocilizumab for rheumatoid arthritis. BSRBR follows for longer periods relatively unselected groups of RA patients on a biological therapy and should be suited to study the occurrence of serious cardiovascular events.

An extension to the BSRBR to recruit a cohort of tocilizumab (RoActemra)-treated patients provides an invaluable opportunity to assess the efficacy and comparative safety outcomes of this additional agent in clinical practice, particularly cardiovascular events (as above), as well as malignancy and serious infection. Some patients already registered with BSRBR are likely to switch to tocilizumab if their current therapy is not effective, but there will also be a group of patients who have not been registered with BSRBR at all because as they started biologic therapy after BSRBR had completed recruitment of etanercept, infliximab and adalimumab patients (May 2005 onwards).

It is proposed that BSRBR recruits 2600 patients who are receiving tocilizumab over a three-year period (see page 5 of the protocol for sample size calculations). Baseline data collection and follow-up will be the same as for the current biologic 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 biologic therapies are referred to as "new therapies". For patients who switch to tocilizumab from other biologic therapies, it is proposed that BSRBR collect disease measures and medication at time of the switch (Biologic supplementary switch form). The consultant baseline has been modified to include the option of registering the patient as starting tocilizumab, and the follow up questionnaire has been adjusted to collect information on when infusions of tocilizumab are given, as well as the dose of the infusion.

References

[1]National Institute for Health and Clinical Excellence. Final appraisal determination – Tocilizumab for the treatment of rheumatoid arthritis. Issue date: June 2010

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 tocilizumab protocol	Version 1	20/04/2010
Biologic Supplementary Switch Form	Version 1	08/07/2010
Prior Biologic therapy exposure form	Version 2	08/07/2010
Consultant Baseline questionnaire	Version 7	08/07/2010
Consultant follow up questionnaire	Version 7	08/07/2010

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: ..... 13.7.10 .....