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: 23 November 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 (i) the addition of a further biologic drug to the Register (certolizumab pegol) and, (ii) opening of a new anti-TNF comparison cohort.

**(i) Addition of certolizumab pegol to the study**

Biologic therapies have proved effective in clinical trials for treating rheumatoid arthritis (RA) by controlling disease and suppressing disease activity. The British Society for Rheumatology Biologics Register (BSRBR) already monitors the long-term use of anti-TNFα therapies (currently etanercept, infliximab and adalimumab), anakinra (an IL-1 receptor antagonist), rituximab (an anti-B cell therapy) and tocilizumab (an IL-6 inhibitor) 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 anti-TNF certolizumab pegol (trade name Cimzia, produced by UCB) represents a therapeutic alternative to patients for whom either the currently available biologic therapies may be contraindicated or in whom it has been tried and failed.

Recently a new anti-TNF, certolizumab pegol, has been approved for use in RA in the UK. Certolizumab pegol (Cimzia, UCB Pharma) is a pegylated TNF-α-specific Fab fragment of a humanised monoclonal antibody. It binds with high affinity to both soluble and membrane-bound TNF-α, thereby inhibiting TNF-α activity. Results from phase III clinical trials have shown certolizumab to be effective and well tolerated in patients with RA (see references 11-13 in the certolizumab protocol).

An extension to the BSRBR to recruit certolizumab (Cimzia)-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 certolizumab 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 their anti-TNF therapy (either adalimumab, etanercept or infliximab) after BSRBR had completed recruitment of these existing anti-TNF cohorts (2008 onwards).

It is proposed that BSRBR recruit 2000 patients who are receiving certolizumab over a three-year period and collect follow-up data for a minimum of five years (see protocol for sample size calculations (pages 6-7)). Baseline data collection and follow-up will be the same as for the current biologic therapy cohorts.

Since patients starting certolizumab are likely to have tried and failed previous anti-TNF therapy, it is important that BSRBR collect further data on this previous exposure at registration using the "Prior Biologic Therapy Exposure Form" (REC approved 30/01/2007 under the extension to collect a rituximab cohort). For patients who switch to certolizumab but are already registered with the BSRBR as receiving one of the existing anti-TNF therapies, it is proposed that BSRBR collect disease measures and medication at time the patient starts certolizumab (using the Rituximab supplementary switch form – REC approved 30/01/2007 under the extension to collect a rituximab cohort). However, as this form will now be used to collect data for certolizumab in addition to rituximab, we would like to re-name this form "BSRBR Short Baseline Form". The patient information sheet and consent form will not change as the biologic therapies are referred to as "new therapies".

In the UK, the manufacturer of certolizumab (UCB) has agreed a patient access scheme with the Department of Health. Under the scheme, people receive their first 12 weeks of therapy of certolizumab pegol free of charge. NICE technology appraisal guidance states that therapeutic benefit should be measured at 12 weeks of treatment and reconsidered where there is no evidence of such benefit (copy of guidance enclosed). Therefore, we would like to collect the DAS28 measured at 3 months (where available in the clinic notes) at the 6 month follow-up time-point following initial registration with the BSRBR (see the 'DAS28 at 3 months' form which is included with the amendment). This will involve no additional measurements/tests for the patients as it will be recorded in the clinic notes as part of the routine monitoring.

**(ii) New anti-TNF comparison cohort**

Independent of treatment, there is an increased risk of serious infection, malignancy and premature mortality in patients with RA. It is thus fundamentally important to assess not only the risk of these important outcomes 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. However, a high proportion of patients who are eligible to start certolizumab in routine clinical care, will have

already been exposed to other biologic therapies (unless contraindicated) and therefore it is proposed that the certolizumab cohort is compared with two non-certolizumab reference cohorts:

(i) A new prospective comparison cohort of 2000 RA patients starting one of the existing anti-TNF therapies (adalimumab, etanercept, infliximab) recruited from rheumatology centres across the UK (see certolizumab protocol page 5 for further details).

(ii) Retrospective comparison cohort of RA patients receiving non-biologic DMARD therapy (this cohort has already been recruited as part of the BSRBR and are under follow-up)

**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* |
|---|---|---|
| | | |
| BSRBR Protocol | No version number | October 2003 |
| Certolizumab Protocol | ~~1~~ 3 | ~~18/10/2010~~ 15/11/2010 |
| DAS28 at 3 Months Form | 1 | 22/10/2010 |
| Consultant Baseline Questionnaire | 8 | 23/11/2010 |
| Consultant Follow-up Questionnaire | 8 | 23/11/2010 |
| Extension of Follow Up Form | 3 | 04/11/2010 |
| Short Baseline Form | 1 | 04/11/2010 |

**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:* D P M Symmons

*Date of submission:* 29/11/10