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: 16th May 2011

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 <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.

This amendment covers the addition of two questionnaires to the BSR Biologics Register

i) the participant-completed 'BSRBR Work Disability Questionnaire'

ii) the clinician-completed 'DMARD comparison cohort to biologic cohort switch form'

(i) Participant-completed work disability questionnaire:

People with rheumatoid arthritis (RA) are highly likely to suffer disability leading to loss of work productivity [1-3] and data from cross sectional studies have found work disability rates ranging between 13 and 67% depending on duration of disease[4]. The BSRBR has already collected and published preliminary data relating to working status reported by patients with RA participating in the study at baseline and three years. Verstappen et al (2010) demonstrated already high baseline rates of disability in patients on biologic therapy (49%). The results also demonstrated that patients with worse functional ability and a manual job at baseline were more likely to become work disabled by three years[5]. However, the results from our study also demonstrated that patients who responded to treatment with biologic therapy were less likely to develop future work disability. It is remains unclear as to the effect of biologic therapies in preventing new work disability and whether these newer therapies are more likely to reduce the economic burden associated with this disease compared to conventional DMARD therapy both in terms of direct and indirect costs.

In order to understand the association between biologic therapy and work disability in more detail, we would like to collect additional detailed data using a questionnaire that has been based on the validated Work Disability Survey for RA (WPS-RA). The WPS-RA is a validated self-report questionnaire assessing the impact of RA on productivity in the work place and at home and on participation in family, social and leisure activities[6].

Participants in the BSRBR observational study of new drugs for RA currently complete questionnaires on a 6 monthly basis for three years. This includes the EuroQol-5D (EQ-5D) and the Health Assessment Questionnaire (HAQ) as measures of functional status and quality of life. It is proposed patients will complete an additional short questionnaire (sent out directly to the patient at the same time as the HAQ and EQ-5D) at baseline and follow-up to collect information about how the patient's disease affects their ability to work. Currently at baseline, the patient is asked whether they are employed and if so, what job they perform. This information is also collected at the final three year follow-up point. It is understood that arthritis can cause major difficulties to those who perform paid work; in a survey amongst 128 rheumatologists, researchers and patients with arthritic conditions, 96.8% of the participants agreed that work was an important part of the life of an individual with arthritis and there was a strong endorsement for the measurement of both absenteeism and at-work productivity loss in arthritis studies[7]. In addition, patients who are at work may experience difficulty performing their work and be less efficient than normal or less efficient compared to co-workers. This decline in performance at work is known as `at-work productivity loss' (often also referred to as presenteeism) an important outcome not measured before in the BSRBR. The WPS-RA questionnaire has been modified to include additional questions on working hours and change in employment for use in the BSRBR study. Thus, the BSRBR will now be able to collect more detailed information on an important outcome that was not previously measured in the study.

This new questionnaire (titled "BSRBR Work disability questionnaire") consists of two short sections relating to the individual's working status. Answers are described using tick boxes and short free-text answers. If the patient is not currently working, they will only need to complete section 1. These questions will only take a few extra minutes for patients to complete.

(ii) Consultant-completed comparison cohort biologic switch questionnaire:

Also included in this amendment is the 'DMARD comparison cohort to biologic cohort switch form'. This is to enable the re-registration of patients who are already on the study as a DMARD comparison cohort patient as a new biologic patient if they start an anti-TNF drug. There are currently two comparison cohorts in the BSRBR:

a) the BSRBR comparison cohort switch form

Registration to this cohort of biologic naïve patients on DMARD therapy closed in early 2009. However, patients already recruited to this cohort may be started on a biologic agent by their rheumatology consultant and may be eligible to be re-registered with the BSRBR as a biologic patient. The comparison cohort switch form will be used to collect the minimum dataset required to re-register the patient with the BSRBR.

b) The anti-tnf comparison cohort

The opening of an anti-TNF comparison cohort was approved as part of the certolizumab amendment (approved on 20th December 2010) This cohort recruits biologic naïve patients starting either adalimumab, etanercept or infliximab. If a participant in the anti-tnf comparison cohort begins one of the 'new' biologic drugs (certolizumab, tocilizumab, rituximab and so forth) they may be eligible to be re-registered with the BSRBR. The short baseline form (approved as part of the certolizumab amendment) should be used for this type of switch in the study rather than the new DMARD comparison cohort to biologic switch form.

References

1. Dunlop DD, Manheim LM, Yelin EH, Song J, Chang RW. The costs of arthritis. *Arthritis Rheum* 2003;49:101–13.
2. Kavanaugh A. Economic issues with new rheumatologic therapeutics. *Curr Opin Rheumatol*, 2007;19:272– 6.
3. Lundkvist J, Kastang F, Kobelt G. The burden of rheumatoid arthritis and access to treatment: health burden and costs. *Eur J Health Econ* 2008;8 Suppl 2:S49–60.
4. Verstappen SM, Bijlsma JW, Verkleij H et al. Overview of work disability in rheumatoid arthritis patients as observed in cross-sectional and longitudinal surveys. *Arthritis Rheum* 2004;51:488–97.
5. Verstappen, S., Watson, K., Lunt, M., McGrother, K., Symmons, D., Hyrich, K. & BSR Biologics Register (2010). Working status in patients with rheumatoid arthritis, ankylosing spondylitis and psoriatic arthritis: results from the British Society for Rheumatology Biologics Register. *Rheumatology* (Oxford, England), 49(8), 1570-1577.
6. Osterhaus J, Richard L, Purcaru O. Discriminant validity, responsiveness and reliability of the rheumatoid arthritis specific Work Productivity Survey (WPS-RA). *Arthritis Res Ther* 2009;11:R73.
7. , Beaton et al, Measuring worker productivity: Frameworks and MeasuresThe Journal of Rheumatol, 2009; 36: 2100-2109.

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
Notice of Amendment	N/A	
BSRBR Work Disability Baseline Questionnaire	1	04/03/2011
BSRBR Work Disability Follow-up Questionnaire	1	04/03/2011
DMARD comparison cohort to Biologic Switch form	2	08/02/2011

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: ……

Date of submission: ……