



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:	
<i>Name:</i>	Professor Alan Silman
<i>Address:</i>	arc Epidemiology Unit, The University of Manchester, Stopford Building, Oxford Road, Manchester, M13 9PT
<i>Telephone:</i>	0161 275 5041
<i>E-mail:</i>	alan.silman@manchester.ac.uk
<i>Fax:</i>	0161 275 5040

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 15/03/2006
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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 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.

Patients taking part in this observational study of new drugs (anti-TNF α) for rheumatoid arthritis are sent out questionnaires on a 6 monthly basis for three years. This patient follow-up questionnaire currently contains the Health Assessment Questionnaire (which measures physical function) and the SF-36 (which is a health survey giving physical and mental health component scores).

However, we are unable to accurately calculate the cost effectiveness of anti-TNF α therapy using the current instruments. The SF-6D, a health utility measure based on the SF-36 and

developed for use in economic analysis has a floor effect which limits its ability to distinguish between states of severe health¹. It has been shown that the EQ-5D measure is better than the SF-6D at distinguishing severe health states². Consequently in previous cost-effectiveness analysis using this study [Brennan, Bansback & Nixon], predicted values of the EQ-5D mapped from the HAQ questionnaire³ were preferred to the actual values from the directly measured SF-6D, despite the loss of accuracy. Therefore, we are proposing to add the EuroQol (EQ-5D) to the patient follow-up questionnaire.

The EQ-5D is a standardised instrument for use as a measure of health outcome. It is applicable to a wide range of health conditions and treatments, and has been validated specifically in patients with rheumatoid arthritis^{4,5}. The EQ-5D instrument has been expressly developed for application in cost effectiveness analysis.

The EQ-5D consists of five descriptive questions relating to the individual's health state and is described using tick boxes. The EQ-5D also contains a visual analogue scale (VAS) for the individual to score their current health state. These questions will only take a few extra minutes for patients to complete and will be completed by both the anti-TNF cohort and the comparison cohort.

Currently the HAQ and SF-36 questionnaires are completed in clinic at baseline. Due to the large number of centres in the UK (n=250 hospitals) registering new patients, we propose to add the EQ-5D to the patient baseline questionnaire which is sent out directly to patients once they start in the study. This will be in exactly the same format as in the follow-up questionnaire.

- (1) Brazier J, Roberts J, Tsuchiya A, Busschbach J. A comparison of the EQ-5D and SF-6D across seven patient groups. *Health Economics* 2004; 13:873-884.
- (2) Marra CA, Esdaile JM, Guh D, Kopec JA, Brazier JE, Koehler BE et al. A comparison of four indirect methods of assessing utility values in rheumatoid arthritis. *Med Care* 2004; 42:1125-1131.
- (3) Bansback N, Marra C, Tsuchiya A, Anis AH, Hammond T, Brazier J. Using the health assessment questionnaire to estimate preference-based single indices in patients with rheumatoid arthritis. *Rheumatology (Oxford)* 2005.
- (4) Hurst NP, Jobanputra P, Hunter M, Lambert M, Lochhead A, Brown H. Validity of Euroqol--a generic health status instrument--in patients with rheumatoid arthritis. *Economic and Health Outcomes Research Group. British Journal of Rheumatology* 1994; 33:655-662.
- (5) Hurst NP, Kind P, Ruta D, Hunter M, Stubbings A. Measuring health-related quality of life in rheumatoid arthritis: validity, responsiveness and reliability of EuroQol (EQ-5D). *British Journal of Rheumatology* 1997; 36:551-559.

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

<i>Document</i>	<i>Version</i>	<i>Date</i>
Patient follow-up Questionnaire	Version 5	15/03/2006

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: