



# 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>.

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|---------------------------------------|--|
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|  |   |
|--|---|
| <b>Full title of study:</b>  | British Society for Rheumatology Biologics Register |
| <b>Name of main REC:</b>   | North West MREC                                     |
| <b>REC reference number:</b>   | MREC 00/8/53  |
| <b>Date study commenced:</b>   | October 2001  |
| <b>Protocol reference (if applicable), current version and date:</b> | 06/10/2003  |
| <b>Amendment number and date:</b>                                    |   |

**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.

**Planned changes**

1. Using data already collected as part of the BSR Biologics Register, identify patients with physician-reported pulmonary fibrosis (a fibrotic lung disease sometimes associated with rheumatoid arthritis, also known as rheumatoid arthritis-associated interstitial lung disease (RA-ILD)).
2. **Collect all supporting information on baseline and incident RA-ILD from investigations already performed (Chest x-ray reports, pulmonary function test reports, lung biopsy reports, broncho-alveolar lavage reports and hard copies of computer tomography (CT) scans) from consultant rheumatologists.** Patients have already consented to collection of further clinical information from their medical records. No additional investigations will be requested.

3. CT scans will be read by a consultant radiologist with an interest in interstitial lung disease (ILD) to assess the subtype and the severity of the lung fibrosis. The patient's identity on the scans will be replaced by a unique study number, blinding the reader to the patient's identity.
4. The additional information on baseline RA-ILD will be used to predict outcome including mortality and serious respiratory adverse events. These outcomes are already captured in the current study design.

### **Supporting Scientific Information**

#### **Background**

Rheumatoid arthritis (RA) is a chronic systemic inflammatory disease typified by its joint involvement with consequent pain, swelling, stiffness and deformity. Whilst the primary site of pathology is the synovium (joint lining), joint symptoms are commonly accompanied by extra-articular manifestations of the disease. Multiple body systems can be affected, one of the most frequent sites being the lungs.

There are many types of lung disease associated with RA, including RA-ILD / pulmonary fibrosis, respiratory infections, malignancy, airways disease, vessel disease, pleural disease, pulmonary nodules and pulmonary vasculitis. Of these, RA-ILD is thought to be the commonest with estimated prevalence rates from between 6-52% depending upon definition.

The natural history of RA-ILD is not widely researched, though patients with RA-ILD are thought have a poor prognosis. Preliminary analysis of the BSRBR data confirms that patients with RA-ILD have a mortality rate greater than three-fold higher than similar RA patients without ILD. Two small outcome studies, both following less than 30 patients, estimate a 20% mortality at 2 years and a 48% mortality at 28 months. To date, there are no robust predictors of outcome in RA-ILD. One of the most likely candidates for prediction of outcome is the clinico-patho-radiological subtype. In idiopathic interstitial pneumonia (ILD without a known cause or associated disease), there has been much more extensive research: idiopathic pulmonary fibrosis (IPF) / usual interstitial pneumonia (UIP) has a worse prognosis than non-specific interstitial pneumonia (NSIP). RA-ILD has similar clinico-patho-radiological groups, but it is not known if they behave in the same way.

TNF $\alpha$  is implicated as a mediator of ILD. Inhibition of TNF in patients with RA-ILD has been associated with stabilisation or improvement in the lung disease. However, there are also case reports of rapid fatal deterioration of RA-ILD with anti-TNF therapy. No prospective studies have examined the impact of anti-TNF therapy on RA-ILD.

Due to the large size of this national cohort and the prospective capture of all serious adverse events, the BSRBR offers a unique opportunity to study the factors governing the occurrence and progression of RA-ILD, including anti-TNF drugs.

#### **Hypotheses:**

Clinico-patho-radiological subtype of RA-ILD (UIP vs non-UIP) predicts progression of disease

Treatment with anti-TNF $\alpha$  drugs will alter the progression of RA-ILD

#### **Aims:**

To determine the influence of clinico-patho-radiological subtype and severity of RA-ILD upon respiratory outcome

**Objectives:**

1. To ascertain prevalence and incidence rates of patients with physician-reported RA-ILD who are already consented to take part in the BSRBR (a study to monitor the long-term safety of biologic agents in rheumatic diseases).
2. To collect all available evidence leading to the diagnosis of RA-ILD prior to the point of consent and registration (Chest x-ray reports, pulmonary function test reports, lung biopsy reports, broncho-alveolar lavage reports and hard copies of computer tomography (CT) scans), plus similar information on serious respiratory adverse events identified within the prospective follow-up of the BSRBR.
3. To verify the diagnosis of RA-ILD by obtaining 2.
4. To determine the clinico-patho-radiological subtype (UIP vs non-UIP) in the verified cases
5. To examine factors predicting respiratory outcome of patients with RA-ILD at baseline, including clinico-patho-radiological subtype and severity of RA-ILD

**Methods:**

1. The BSRBR is an ongoing national prospective observational study assessing the medium- to long-term safety of biologic drugs in the treatment of rheumatic diseases. To 13/12/05, there have been 14192 patients registered. Extensive clinical information is collected at baseline and at six-monthly follow-up intervals. Patients with physician-reported pulmonary fibrosis / RA-ILD will be identified from the register, and can then be followed to determine adverse events including death.
2. Consultants will be contacted by letter requesting supporting information for the diagnosis of pulmonary fibrosis, including hard copies of CT scans if available. Patients have already consented to their specialist providing information from their medical records to the researchers. **Additional work for the consultant / rheumatology specialist nurse entails compilation of supporting information from clinical notes or hospital departments (radiology, respiratory physiology, histopathology) and postage of compiled information to Manchester.** Once received, any patient details will be replaced with a unique identification number, thus concealing patient details from investigators reading scans or reports.
3. CT scans will be read by a consultant radiologist with a special interest in ILD and will be categorised into 'no ILD' or 'ILD', and in the latter group to 'UIP' or 'non-UIP' with an ILD severity score using verified instruments. Other supporting information will be collated. These variables will be used to predict outcome in patients treated with and without anti-TNF drugs. The primary outcome measure will be mortality and the secondary outcome measure will be serious respiratory adverse events.

**Sample sizes:**

To 01/09/05 there were 312 patients with RA and physician-reported pulmonary fibrosis at baseline. 280 of these were treated with biologic drugs and 32 were in the comparison group, treated with traditional disease-modifying anti-rheumatic drugs (DMARDs). This number will increase as more patients are recruited to the register. Based on the few small studies of RA-ILD clinico-patho-radiological subtype, we might expect 12-56% to have UIP. For the purposes of the power calculation, we will estimate required follow-up time for the non-UIP group based upon estimated ratios of non-UIP to UIP of 80:20. A proportion of 50:50 would require less follow-up data.

The primary aim is to detect a difference between the two groups and outcome (mortality and serious adverse events) within the whole RA-ILD cohort and furthermore within the anti-TNF $\alpha$  group alone. A conservative 'minimum clinically significant difference' would be a two-fold increase in mortality. Sample size calculation is based on an 80% power and 5% significance.

*Mortality:* To September 2005, there have been 33 deaths in patients with RA-ILD. Of these, 30 were treated with anti-TNF therapy and 3 with traditional DMARDs. The overall death rate for patients with RA-ILD is 58/1000pyrs, and for the anti-TNF and comparison group,

respectively, are 55/1000pyrs and 97/1000pyrs. For comparison, the death rate for patients with RA but no ILD is 13/1000pyrs. As there are no estimates for death rates of non-UIP RA-ILD in the literature, so we will assume the death rate for the non-UIP cohort to be 58/1000 pyrs. Using this rate with a relative risk of 2, we would need to have 175 person years of follow-up in the UIP cohort to give power >80%. If the balance is 80:20 non-UIP:UIP, we would need a total of 875 pyrs for the whole cohort. Assuming we obtain a further 1 year follow-up for all patients but no further recruitment, we would need to read and categorise 308 HRCTs. As HRCTs will be available only in a proportion of patients diagnosed with baseline RA-ILD (estimated at ~60%), we will need to request additional information from the consultants for verification and categorisation from around 500 cases.

**Time scale:** It is estimated that the collection of information and scans supporting the diagnosis of pulmonary fibrosis will take until the end of 2006, when the target 4000 comparison patients will be reached. Once the HRCT scans are read, analyses can be performed to assess mortality at set intervals e.g 1, 2, 5 and 10 year mortality,

**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> |
|-------------------|----------------|-------------|
| Consultant letter | 1              | 27/02/2006  |
|                   |                |             |
|                   |                |             |

**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:* .....

*Date of submission:* .....