## APPLICANT'S CHECKLIST

**All studies except clinical trials of investigational medicinal products**

| | |
|---|---|
| REC Ref: | MREC 00/8/53 |
| Short Title of Study: | Toxicity from Anti−TNF Therapy |
| CI Name: | Professor Alan Silman |
| Sponsor: | |

**Please complete this checklist and send it with your application**

- Send ONE copy of each document (except where stated)
- ALL accompanying documents must bear version numbers and dates (except where stated)
- When collating please do NOT staple documents as they will need to be photocopied.

| Document | Enclosed? | Date | Version | Office use |
|---|---|---|---|---|
| Covering letter on headed paper | ○ Yes ○ No | | | |
| NHS REC Application Form, Parts A&B | Mandatory | | | |
| NHS REC Application Form, Part C (SSA) | ○ Yes ○ No | | | |
| Research protocol (6 copies) or project proposal | Mandatory | | | |
| Summary C.V. for Chief Investigator (CI) | Mandatory | | | |
| Summary C.V. for supervisor (student research) | ○ Yes ○ No | | | |
| Research participant information sheet (PIS) | ○ Yes ○ No | | | |
| Research participant consent form | ○ Yes ○ No | | | |
| Letters of invitation to participants | ○ Yes ○ No | | | |
| GP/Consultant information sheets or letters | ○ Yes ○ No | | | |
| Statement of indemnity arrangements | ○ Yes ○ No | | | |
| Letter from sponsor | ○ Yes ○ No | | | |
| Letter from statistician | ○ Yes ○ No | | | |
| Letter from funder | ○ Yes ○ No | | | |
| Referees' or other scientific critique report | ○ Yes ○ No | | | |
| Summary, synopsis or diagram (flowchart) of protocol in non−technical language | ○ Yes ○ No | | | |
| Interview schedules or topic guides for participants | ○ Yes ○ No | | | |
| Validated questionnaire | ○ Yes ○ No | | | |
| Non−validated questionnaire | ○ Yes ○ No | | | |
| Copies of advertisement material for research participants, e.g. posters, newspaper adverts, website. For video or audio cassettes, please also provide the printed script. | ○ Yes ○ No | | | |

## WELCOME TO THE NHS RESEARCH ETHICS COMMITTEE APPLICATION FORM

This page is important. An application form specific to your project will be created from the answers you give.

**1. Select one research category from the list below:**

- ○ Clinical trials of investigational medicinal products (including phase 1 drug development)
- ○ Clinical investigations of medical devices
- ○ Research administering questionnaires for quantitative analysis
- ○ Research involving qualitative methods only
- ○ Research limited to taking and working with new samples
- ○ Non–interventional research

**If your work does not fit any of these categories, select the option below:**

- ◉ Other research

**1a. Please answer the following questions:**

| | | |
|---|---|---|
| a) Does your study involve the use of any radiation? | ○ Yes | ◉ No |
| b) Will you be taking new samples? | ○ Yes | ◉ No |
| c) Will you be using existing samples? | ○ Yes | ◉ No |

**2. Is your research confined to one site?**

○ Yes ◉ No

**3. Does your research involve work with prisoners?**

○ Yes ◉ No

**4. Does your research involve adults unable to consent for themselves through physical or mental incapacity?**

○ Yes ◉ No

**5. Is your work an educational project?**

○ Yes ◉ No

**6. Is your project an audit or service evaluation?**

○ Yes ◉ No

# NHS Research Ethics Committee NHS
# Application form

**This form should be completed by the Chief Investigator, after reading the guidance notes. See glossary for clarification of different terms in the application form.**

**Short title and version number:** (maximum 70 characters – this will be inserted as header on all forms)
Toxicity from Anti–TNF Therapy

**Name of NHS Research Ethics Committee to which application for ethical review is being made:**
North West MREC

**Project reference number from above REC:** MREC 00/8/53
**Submission date:** 20/08/2005

## PART A: Introduction

### A1. Title of the research

Full title: Prospective Observational Study of the Long–Term Hazards of anti–TNF Therapy in rheumatoid arthritis

Key words: rheumatoid arthritis, anti–TNF, observational

### A2. Chief Investigator


| | |
|---|---|
| Title: | Professor |
| Forename/Initials: | Alan |
| Surname: | Silman |
| Post: | Professor of Rheumatic Disease Epidemiology |
| Qualifications: | MSc MD FRCP FFPHM |
| Organisation: | ARC Epidemiology Unit |
| Address: | The University of Manchester |
| | Stopford Building, Oxford Road |
| | Manchester |
| Post Code: | M13 9PT |
| E–mail: | alan.silman@manchester.ac.uk |
| Telephone: | 0161 275 5041 |
| Fax: | 0161 275 5043 |


*A copy of a current CV (maximum 2 pages of A4) for the Chief Investigator must be submitted with the application*

### A3. Proposed study dates and duration

Start date: 01/10/2001
End date:
Duration: Months: ; Years: 5

**A4. Primary purpose of the research:** *(Tick as appropriate)*

- ☐ Commercial product development and/or licensing
- ☑ Publicly funded trial or scientific investigation
- ☐ Educational qualification
- ☐ Establishing a database/data storage facility
- ☐ Other

**A6. Does this research require site–specific assessment (SSA) of each research site?** (Advice can be found in the guidance notes on this topic.)

◉ Yes ○ No

*If No, please justify:*

*If Yes, Part C of the form will need to be completed for each research site and submitted for SSA to the relevant Local Research Ethics Committee. Do not submit Part Cs for other sites until the application has been booked for review and validated by the main Research Ethics Committee.*

*Management approval to proceed with the research will be required from the RDDepartment for each NHS care organisation in which research procedures are undertaken. This applies whether or not the research is exempt from SSA.*

**PART A: Section 1**

**A7. What is the principal research question/objective?** *(Must be in language comprehensible to a lay person.)*

The hypothesis will be tested that biologic therapy in patients with rheumatic diseases increases the risk of malignancy and severe infection. In developing the methods of a study to test this hypothesis it is assumed that any increased risk would become apparent within 5 years of starting therapy

The following primary endpoints will be evaluated:
(1) any malignancy
(2) any lymphoproliferative malignancy
(3) any infection requiring hospitalisation
(4) death

**A8. What are the secondary research questions/objectives?** *(If applicable, must be in language comprehensible to a lay person.)*

The following subsidary hypotheses will be tested:
(1) any increased risk is related to dose or duration of therapy
(2) there are specifically indentifiable disease characteristics that act synergistically to increase the risk
(3) therapy with multiple biologic agents act synergistically to increase the risk

**A9. What is the scientific justification for the research? What is the background? Why is this an area of importance?***(Must be in language comprehensible to a lay person.)*

A number of new, so called 'biological' agents have recently been licensed for disease suppressive therapy in rheumatoid and related inflammatory arthropathies. Currently, the most notable are those designed to block the action of TNFμ: etanercept and infliximab. The anti TNFμ drugs have been shown to be of benefit in achieving disease control in rheumatoid arthritis and juvenile idiopathic arthritis for up to one year. Data also suggest they may be effective in slowing the process of erosive damage. Their efficacy over the longer term needs to be assessed. Data from clinical trials have reported relatively low levels of toxicity with these drugs and the incidence of adverse events or side effects during therapy, at least in the first few months of therapy, seem to be acceptably low. It might be expected that these agents would impair the immune response to infection but data from isolated case reports of serious infection are difficult to interpret. Similarly there are no data available on the magnitude of any increased risk of lymphoproliferative malignancy in the long−term, although a few cases have been reported. Clinical trials of new agents also exclude many groups of patients at higher risk of infection, for example those with co−morbidities such as diabetes. In routine practice the occurrence of such events may be higher.

It is important to remember, however, that there is an increased risk both of serious infection and lymphoproliferative malignancy in patients with rheumatoid arthritis and other connective tissue diseases, independent of whatever treatment they have received. Thus, it has been clearly established that there is a substantial increased risk of non−Hodgkin's lymphoma in patients with rheumatoid arthritis, associated with long standing active disease. Similarly, patients with rheumatoid arthritis are at a significantly increased risk of serious infection, and indeed infection is often cited as one of the major causes of excess deaths in this disorder. Thus the patients most likely to receive the new agents are already at increased risk of infection and malignancy. It is therefore fundamentally important not just to document the occurrence of these events 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.

**A10. Give a full summary of the purpose, design and methodology of the planned research, including a brief explanation of the theoretical framework that informs it. It should be clear exactly what will happen to the research participant, how many times and in what order. Describe any involvement of research participants, patient groups or communities in the design of the research.**

*This section must be completed in language comprehensible to the lay person. It must also be self−standing as it will be replicated in any applications for site−specific assessment on Part C. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.*

The study proposed is a series of prospective cohort studies comparing the risk of development, over 5 years, of the endpoint between: (i) an exposed group of patients with one of a list of defined rheumatic disorders newly exposed to a

biologic drug and (ii) a comparison cohort of rheumatoid arthritis patients with similar disease characteristics exposed to other, but non−biologic, therapies. It is envisaged that there will be a number of exposed cohorts studied, each defined by starting therapy with a particular agent, but that the comparison would be with the same group of non−biologic treated subjects.

Exposed Cohort

For each biologic drug the exposed cohort will be patients with a rheumatic disease (the most common being rheumatoid arthritis), newly starting therapy with that biologic agent. Inclusion criteria for such subjects are:

(i) patients with rheumatoid arthritis should either satisfy ACR classification criteria at the time of registration or be classified as having been diagnosed with RA by the consultant rheumatologist.
(ii) age 16 – 75.
(iii) willingness to give informed consent for long term follow−up including access to all medical records.
(iv) minimum of one treatment with a biologic agent.

External validity will be maximised by attempting to ascertain all patients, newly treated with that biologic agent. The support of the BSR with help from the pharmaceutical industry will be necessary to ensure maximal recruitment.

Recruitment will be co−ordinated at a national level. The study will be based in the United Kingdom and the Republic of Ireland.

Non−exposed Cohort

It is accepted that patients treated with biologic therapy will be those with more severe disease. It is assumed, based on both financial grounds, and random variation in clinical practice, that there will be considerable overlap in the severity profile between those patients exposed to a biologic agent and those not exposed. A number of rheumatological centres, representing a broad mix of secondary and tertiary care service provision, and geographical and socio−demographic diversity have been recruited. These include Belfast, Glasgow, Leeds, London (GKT) Stoke−on−Trent, Derby, Norwich and Poole. Other centres have been approached including Manchester Royal Infirmary, Macclesfield District General Hospital, Christchurch Hospital and St Helen's Hospital. Patients will be eligible to be included as non−exposed if they have RA and were started or continued on a new, non−biologic, disease modifying drug within the previous six months.

Each of the centres listed above will submit to the co−ordinating centre, baseline information on all new non−biologic therapy patients together with other relevant clinical and laboratory data. The selected subjects will have already been asked by their local centre for their informed consent to be followed up, as for the exposed cohort.

Sample Size

The aim is to recruit 4000 biologic patients per drug and 4000 traditional DMARD therapy patients − this will allow for enough follow−up time to detect a two−fold increase in lymphoma, the rarest event of interest.

Consent and data collection

It will be the responsibility of the referring rheumatologist to obtain patient consent prior to notification. Patient information sheets, consent forms and a copy of this protocol will be made available on the ARC Epidemiology Unit's and the BSR's website or directly from the BSR. Receipt of notification would then act as the initiating event for the collection of the baseline data, recruitment of comparison subjects and all necessary follow up.

Follow−up

Patients are followed up via questionnaires to the rheumatologist on a 6 monthly basis for three years and annually for two years. Patients are also sent a questionnaire and diary directly to their homes on a 6 monthly basis for three years. All patients are flagged with the Office for National Statistics (ONS) for malignancy and mortality.

**A11. Will any intervention or procedure, which would normally be considered a part of routine care, be withheld from the research participants?**

○ Yes ◉ No

**A12. Give details of any clinical intervention(s) or procedure(s) to be received by research participants over and above those which would normally be considered a part of routine clinical care.** *(These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material.)*

| Additional Intervention | Average number per patient | | Average time taken (mins/hours/days) | Details of additional intervention or procedure, who will undertake it, and what training they have received. |
|---|---|---|---|---|
| | Routine Care | Research | | |
| | | | | |

**A13. Give details of any non−clinical research−related intervention(s) or procedure(s).** *(These include interviews, non−clinical observations and use of questionnaires.)*

| Additional Intervention | Average number per patient | Average time taken (mins/hours/days) | Details of additional intervention or procedure, who will undertake it, and what training they have received. |
|---|---|---|---|
| Other Questionnaire | 9 | 15 | Questionnaires are sent out directly to the rheumatolgist /nurse on a 6 monthly basis for three years and then annually for two years to capture any changes in therapy, disease activity and adverse events |
| Postal questionnaire to home | 9 | 15 | Patients are sent a questionnaire which measures functional activity (HAQ) and health assessment (SF−36)along with a diary to record hospitalisations, new drugs and referrals on a 6 monthly basis for three years |

**A14. Will individual or group interviews/questionnaires discuss any topics or issues that might be sensitive, embarassing or upsetting, or is it possible that criminal or other disclosures requiring action could take place during the study (e.g. during interviews/group discussions, or use of screening tests for drugs)?**

○ Yes ◉ No

*The Information Sheet should make it clear under what circumstances action may be taken*

**A15. What is the expected total duration of participation in the study for each participant?**

Patients will be sent questionnaires for the first three years only. They will continue to be followed via their rheumatologist for a further two years. They will be flagged with ONS for malignancy and mortality

**A16. What are the potential adverse effects, risks or hazards for research participants either from giving or withholding medications, devices, ionising radiation, or from other interventions (including non−clinical)?**

N/A

**A17. What is the potential for pain, discomfort, distress, inconvenience or changes to lifestyle for research participants?**

**A18. What is the potential for benefit to research participants?**

N/A

**A19. What is the potential for adverse effects, risks or hazards, pain, discomfort, distress, or inconvenience to the researchers themselves?** *(if any)*

N/A

**A20. How will potential participants in the study be (i) identified, (ii) approached and (iii) recruited?**
*Give details for cases and controls separately if appropriate:*

**A21. Where research participants will be recruited via advertisement, give specific details.**

☐ Not Applicable

*If applicable, enclose a copy of the advertisement/radio script/website/video for television (with a version number and date).*

**A22. What are the principal inclusion criteria?***(Please justify)*

**A23. What are the principal exclusion criteria?***(Please justify)*

**A24. Will the participants be from any of the following groups?***(Tick as appropriate)*

☐ Children under 16
☐ Adults with learning disabilities
☐ Adults who are unconscious or very severely ill
☐ Adults who have a terminal illness
☐ Adults in emergency situations
☐ Adults with mental illness (particularly if detained under Mental Health Legislation)
☐ Adults with dementia
☐ Prisoners
☐ Young Offenders
☐ Adults in Scotland who are unable to consent for themselves
☐ Healthy Volunteers
☐ Those who could be considered to have a particularly dependent relationship with the investigator, e.g. those in care homes, medical students
☐ Other vulnerable groups

*Justify their inclusion.*

**A25. Will any research participants be recruited who are involved in existing research or have recently been involved in any research prior to recruitment?**

○ Yes ○ No ◉ Not Known

*If Yes, give details and justify their inclusion. If Not Known, what steps will you take to find out?*

**A26. Will informed consent be obtained from the research participants?**

◉ Yes ○ No

*If Yes, give details of who will take consent and how it will be done. Give details of any particular steps to provide information (in addition to a written information sheet) e.g. videos, interactive material.*

*If participants are to be recruited from any of the potentially vulnerable groups listed in A24, give details of extra steps taken to assure their protection. Describe any arrangements to be made for obtaining consent from a legal representative.*

*If consent is not to be obtained, please explain why not.*

*Copies of the written information and all other explanatory material should accompany this application.*

**A27. Will a signed record of consent be obtained?**

◉ Yes ○ No

*If Yes, attach a copy of the information sheet to be used, with a version number and date.*

**A28. How long will the participant have to decide whether to take part in the research?**

**A29. What arrangements have been made for participants who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?** *(e.g. translation, use of interpreters etc.)*

As the questionnaires are completed as part of routine clinical practice, arrangements are made at a local level for this if necessary.

**A30. What arrangements are in place to ensure participants receive any information that becomes available during the course of the research that may be relevant to their continued participation?**

**A31. Does this study have or require approval of the Patient Information Advisory Group (PIAG) or other bodies with a similar remit?***(see the guidance notes)*

◉ Yes ○ No

*If Yes, give details*

**A32a. Will the research participants' General Practitioner be informed that they are taking part in the study?**

◉ Yes ○ No

*If Yes, enclose a copy of the information sheet/letter for the GP with a version number and date.*

**A32b. Will permission be sought from the research participants to inform their GP before this is done?**

◉ Yes ○ No

*If No to either question, explain why not*

*It should be made clear in the patient information sheet if the research participant's GP will be informed.*

**A33. Will individual research participants receive any payments for taking part in this research?**

◉ Yes ○ No

*If Yes, indicate how much and on what basis this has been decided:*

**A34. Will individual research participants receive *reimbursement of expenses* or any other *incentives or benefits* for taking part in this research?**

◉ Yes ○ No

*If Yes, indicate how much and on what basis this has been decided:*

**A35. What arrangements have been made to provide indemnity and/or compensation in the event of a claim by, or on behalf of, participants for *negligent* harm?**

*Please forward copies of the relevant documents.*

**A36. What arrangements have been made to provide indemnity and/or compensation in the event of a claim by, or on behalf of, participants for *non–negligent* harm?**

*Please forward copies of the relevant documents.*

**A37. How is it intended the results of the study will be reported and disseminated?** *(Tick as appropriate)*

☐ Peer reviewed scientific journals
☐ Internal report
☐ Conference presentation
☐ Other publication
☐ Submission to regulatory authorities

- ☐ Access to raw data and right to publish freely by all investigators in study or by Independent Steering Committee on behalf of all investigators
- ☐ Written feedback to research participants
- ☐ Presentation to participants or relevant community groups
- ☐ Other/none e.g. Cochrane Review, University Library

**A38. How will the results of research be made available to research participants and communities from which they are drawn?**

**A39. Will the research involve any of the following activities at any stage (including identification of potential research participants)?** *(Tick as appropriate)*

- ☐ Examination of medical records by those outside the NHS, or within the NHS by those who would not normally have access
- ☐ Electronic transfer by magnetic or optical media, e−mail or computer networks
- ☐ Sharing of data with other organisations
- ☐ Export of data outside the European Union
- ☐ Use of personal addresses, postcodes, faxes, e−mails or telephone numbers
- ☐ Publication of direct quotations from respondents
- ☐ Publication of data that might allow identification of individuals
- ☐ Use of audio/visual recording devices
- ☐ Storage of personal data on any of the following:
  - ☐ Manual files including X−rays
  - ☐ NHS computers
  - ☐ Home or other personal computers
  - ☐ University computers
  - ☐ Private company computers
  - ☐ Laptop computers

*Further details:*

**A40. What measures have been put in place to ensure confidentiality of personal data? Give details of whether any encryption or other anonymisation procedures have been used and at what stage:**

**A41. Where will the analysis of the data from the study take place and by whom will it be undertaken?**

**A42. Who will have control of and act as the custodian for the data generated by the study?**

**A43. Who will have access to the data generated by the study?**

**A44. For how long will data from the study be stored?**

Years Months

*Give details of where they will be stored, who will have access and the custodial arrangements for the data:*

**A45–1. How has the scientific quality of the research been assessed?***(Tick as appropriate)*

- ☐ Independent external review
- ☐ Review within a company
- ☐ Review within a multi–centre research group
- ☐ Internal review (e.g. involving colleagues, academic supervisor)
- ☐ None external to the investigator
- ☐ Other, e.g. methodological guidelines *(give details below)*

*Justify and describe the review process and outcome. If the review has been undertaken but not seen by the researcher, give details of the body which has undertaken the review:*

*If you are in possession of any referees' comments or other scientific critique reports relevant to the proposed research, these must be enclosed with the application.*

**A45–2. Has the protocol submitted with this application been the subject of review by a statistician independent of the research team?***(Select one of the following)*

- ◉ Yes – copy of review enclosed
- ○ Yes – details of review available from the following individual or organisation (give contact details below)
- ○ No – justify below

**A48. What is the primary outcome measure for the study?**

**A49. What are the secondary outcome measures?***(if any)*

**A50. How many participants will be recruited?**
*If there is more than one group, state how many participants will be recruited in each group. For international studies, say how many participants will be recruited in the UK and in total.*

**A51. How was the number of participants decided upon?**

*If a formal sample size calculation was used, indicate how this was done, giving sufficient information to justify and reproduce the calculation.*

**A52. Will participants be allocated to groups at random?**

◉ Yes ○ No

*If yes, give details of the intended method of randomisation:*

**A53. Describe the methods of analysis (statistical or other appropriate methods, e.g. for qualitative research) by which the data will be evaluated to meet the study objectives.**

**A54. Where will the research take place?** *(Tick as appropriate)*

☐ UK
☐ Other states in European Union
☐ Other countries in European Economic Area
☐ Other

*If Other, give details:*

**A55. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK, the European Union or the European Economic Area?**

○ Yes ◉ No

**A56. In how many and what type of host organisations (NHS or other) in the UK is it intended the proposed study will take place?**

*Indicate the type of organisation by ticking the box and give approximate numbers if known:*

| | Number of organisations |
|---|---|
| ☐ Acute teaching NHS Trusts | |
| ☐ Acute NHS Trusts | |
| ☐ NHS Primary Care Trusts or Local Health Boards in Wales | |
| ☐ NHS Trusts providing mental healthcare | |
| ☐ NHS Health Boards in Scotland | |
| ☐ HPSS Trusts in Northern Ireland | |
| ☐ GP Practices | |
| ☐ NHS Care Trusts | |

☐ Social care organisations
☐ Prisons
☐ Independent hospitals
☐ Educational establishments
☐ Independent research units
☐ Other (give details)

*Other:*

**A57. What arrangements are in place for monitoring and auditing the conduct of the research?**

**Will a data monitoring committee be convened?**

◉ Yes ○ No

*If Yes, details of membership of the data monitoring committee (DMC), its standard operating procedures and summaries of reports of interim analyses to the DMC must be forwarded to the NHS Research Ethics Committee which gives a favourable opinion of the study.*

**What are the criteria for electively stopping the trial or other research prematurely?**

**A58. Has external funding for the research been secured?**

◉ Yes ○ No

**If Yes, give details of funding organisation(s) and amount secured and duration:**

Organisation:
Address:

Post Code:
UK contact:
Telephone: Fax:
E−mail:
Amount (£): Duration: Months

**A59. Has the funder of the research agreed to act as sponsor as set out in the Research Governance Framework?**

◉ Yes ○ No

**Has the employer of the Chief Investigator agreed to act as sponsor of the research?**

◉ Yes ○ No

**Sponsor***(must be completed in all cases)*

Name of organisation which will act as sponsor for the research:

Status:

○ NHS or HPSS care organisation ◉ Academic ○ Pharmaceutical industry ○ Medical device industry ○ Other

*If Other, please specify:*

Address:

Post Code:
Telephone: Fax:
E–mail:

*The responsibilities of the sponsor may be shared between co–sponsors. If this applies, name the lead sponsor for the REC application in this box and enclose a letter giving further details of co–sponsors and their responsibilities.*

**Sponsor's UK contact point for correspondence with the main REC**

Title: Forename/Initials: Surname:

Address:

Post Code:
Telephone: Fax:
E–mail:

**A60. Has any responsibility for the research been delegated to a subcontractor?**

◉ Yes ○ No

*If Yes, give details including:*
*Name of research contract organisation/site management organisation, and summary of delegated responsibility*

**A61. Will individual *researchers* receive any personal payment over and above normal salary for undertaking this research?**

◉ Yes ○ No

*If Yes, indicate how much and on what basis this has been decided:*

**A62. Will individual *researchers* receive any other benefits or incentives for taking part in this research?**

◉ Yes ○ No

*If Yes, indicate how much and on what basis this has been decided:*

**A63. Will the host organisation or the researcher's department(s) or institution(s) receive any payment or benefits in excess of the costs of undertaking the research?**

◉ Yes ○ No

*If Yes, give details:*

**A64. Does the Chief Investigator or any other investigator/collaborator have any direct personal involvement (e.g. financial, share−holding, personal relationship etc.) in the organisation sponsoring or funding the research that may give rise to a possible conflict of interest?**

◉ Yes ○ No

*If Yes, give details:*

**A65. Other relevant reference numbers if known***(give details and version numbers as appropriate):*

Applicant's/organisation's own reference number, e.g. RD(if available):
Sponsor's/protocol number:
Funder's reference number:
International Standard Randomised Controlled Trial Number (ISRCTN):
European Clinical Trials Database (EudraCT) number:
Project website: www.arc.man.ac.uk/webbiologicsreg.htm

**A66. Other key investigators/collaborators***(all grant co−applicants should be listed)*

Title:
Forename/Initials:
Surname:
Post:
Qualifications:
Organisation:
Address:
Telephone:
Fax:
Postcode:
E−mail:

**A67. If the research involves a specific intervention, (e.g. a drug, medical device, dietary manipulation, lifestyle change etc.), what arrangements are being made for continued provision of this for the participant (if appropriate) once the research has finished?**

☐ Not Applicable

## **PART A:** Summary of Ethical Issues

**A68. What do you consider to be the main ethical issues which may arise with the proposed study and what steps will be taken to address these?**

## PART B: Section 1 – List of proposed research sites

*List below all research sites you plan to include in this study. The name of the site is normally the name of the acute NHS Trust, GP practice or other organisation responsible for the care of research participants. In some cases it may be an individual unit, private practice or a consortium – see the guidance notes.*

*Principal Investigators at other sites should apply to the relevant local Research Ethics Committee for site–specific assessment (SSA) using Part C of the application form. Applications for SSA may be made in parallel with the main application for ethical review (once the main REC has validated the application), or following issue of a favourable ethical opinion. Approval for each site will be issued to you by the main REC following SSA.*

**1. Name of the research site:**

**Principal Investigator for the study at this site:**

Title: Forename/Initials: Surname:

Post:

Address:

Postcode:

## PART B: Section 7 – Declaration

– The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

– I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.

– If the research is approved I undertake to adhere to the study protocol, the terms of the full application of which the main REC has given a favourable opinion and any conditions set out by the main REC in giving its favourable opinion.

– I undertake to seek an ethical opinion from the main REC before implementing substantial amendments to the protocol or to the terms of the full application of which the main REC has given a favourable opinion.

– I undertake to submit annual progress reports setting out the progress of the research.

– I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Officer.

– I understand that research records/data may be subject to inspection for audit purposes if required in future.

– I understand that personal data about me as a researcher in this application will be held by the relevant RECs and their operational managers and that this will be managed according to the principles established in the Data Protection Act.

– I understand that the information contained in this application, any supporting documentation and all correspondence with NHS Research Ethics Committees or their operational managers relating to the application, will be subject to the provisions of the Freedom of Information Acts. The information may be disclosed in response to requests made under the Acts except where statutory exemptions apply.

Signature: .....

Date: 20/09/2005 (dd/mm/yyyy)

Print Name: kath Watson

## PART C: Site–Specific Assessment (SSA)

This form should be completed by the Principal Investigator for each site (see glossary)

*Part C should be completed and sent with the relevant enclosures to each NHS Research Ethics Committee, which needs to consider site–specific issues. See guidance notes at the COREC website for further information about the application procedure.*

*The data in this box is populated from Part A.*

**Short title and version number:**
Toxicity from Anti–TNF Therapy

**Name of NHS Research Ethics Committee to which application for ethical review is being made:**
North West MREC

**Project reference number from above REC:** MREC 00/8/53

**Name of NHS REC responsible for SSA:**

**SSA reference (for REC office use only):**

Questions C1, C4, C5, C6, C7, C8 and C13a correspond to questions A1, A2, A65, A10, A12, A13 and A29 on main application form respectively and will populate automatically:

**C1. Title of the research** *(Populated from A1)*

Full title: Prospective Observational Study of the Long–Term Hazards of anti–TNF Therapy in rheumatoid arthritis
Key words: rheumatoid arthritis, anti–TNF, observational

**C2. Who is the Principal Investigator for this study at this site?**

Title: Forename/Initials: Surname:

Post:
Qualifications:
Organisation:
Address:

Post Code:
E–mail:
Telephone:
Fax:

*A copy of a current CV (maximum 2 pages of A4) for the Principal Investigator(s) must be submitted with the application*

**C2–1. Give the names and posts of other investigators or members of the research team responsible to the local Principal Investigator for this site.**
*Include all staff with a significant research role. If the site is a network or consortium, list all participating investigators below.*

Title:
Forename/Initials:
Surname:
Position:
Qualifications:

Role in the research team:

**C3. Indicate the number of trials/projects within the organisation that the local Principal Investigator has been involved with in the previous 12 months:**

**How many are still current (active or recruiting)?**

**C4. Chief Investigator** *(Populated from A2)*


| | |
|---|---|
| Title: | Professor Forename/Initials: Alan Surname: Silman |
| Post: | Professor of Rheumatic Disease Epidemiology |
| Qualifications: | MSc MD FRCP FFPHM |
| Organisation: | ARC Epidemiology Unit |
| Address: | The University of Manchester |
| | Stopford Building, Oxford Road |
| | Manchester |
| Post Code: | M13 9PT |
| E−mail: | alan.silman@manchester.ac.uk |
| Telephone: | 0161 275 5041 |
| Fax: | 0161 275 5043 |


**C5. Other relevant reference numbers if known** *(Populated from A65)*

Applicants/organisation's own reference number, e.g. RD(if available):
Sponsor's/protocol number:
Funder's reference number:
International Standard Randomized Controlled Trial Number (ISRCTN):
European Clinical Trials Database (EudraCT) Number:
Project website: www.arc.man.ac.uk/webbiologicsreg.htm

**C6. Give a full summary of the purpose, design and methodology of the planned research, including a brief explanation of the theoretical framework that informs it. It should be clear exactly what will happen to the research participant, how many times and in what order. Describe any involvement of research participants, patient groups or communities in the design of the research.**
*(Populated from A10)*

The study proposed is a series of prospective cohort studies comparing the risk of development, over 5 years, of the endpoint between: (i) an exposed group of patients with one of a list of defined rheumatic disorders newly exposed to a biologic drug and (ii) a comparison cohort of rheumatoid arthritis patients with similar disease characteristics exposed to other, but non−biologic, therapies. It is envisaged that there will be a number of exposed cohorts studied, each defined by starting therapy with a particular agent, but that the comparison would be with the same group of non−biologic treated subjects.

Exposed Cohort

For each biologic drug the exposed cohort will be patients with a rheumatic disease (the most common being rheumatoid

arthritis), newly starting therapy with that biologic agent. Inclusion criteria for such subjects are:

(i) patients with rheumatoid arthritis should either satisfy ACR classification criteria at the time of registration or be classified as having been diagnosed with RA by the consultant rheumatologist.
(ii) age 16 – 75.
(iii) willingness to give informed consent for long term follow–up including access to all medical records.
(iv) minimum of one treatment with a biologic agent.

External validity will be maximised by attempting to ascertain all patients, newly treated with that biologic agent. The support of the BSR with help from the pharmaceutical industry will be necessary to ensure maximal recruitment.

Recruitment will be co–ordinated at a national level. The study will be based in the United Kingdom and the Republic of Ireland.

Non–exposed Cohort

It is accepted that patients treated with biologic therapy will be those with more severe disease. It is assumed, based on both financial grounds, and random variation in clinical practice, that there will be considerable overlap in the severity profile between those patients exposed to a biologic agent and those not exposed. A number of rheumatological centres, representing a broad mix of secondary and tertiary care service provision, and geographical and socio–demographic diversity have been recruited. These include Belfast, Glasgow, Leeds, London (GKT) Stoke–on–Trent, Derby, Norwich and Poole. Other centres have been approached including Manchester Royal Infirmary, Macclesfield District General Hospital, Christchurch Hospital and St Helen's Hospital. Patients will be eligible to be included as non–exposed if they have RA and were started or continued on a new, non–biologic, disease modifying drug within the previous six months.

Each of the centres listed above will submit to the co–ordinating centre, baseline information on all new non–biologic therapy patients together with other relevant clinical and laboratory data. The selected subjects will have already been asked by their local centre for their informed consent to be followed up, as for the exposed cohort.

Sample Size

The aim is to recruit 4000 biologic patients per drug and 4000 traditional DMARD therapy patients – this will allow for enough follow–up time to detect a two–fold increase in lymphoma, the rarest event of interest.

Consent and data collection

It will be the responsibility of the referring rheumatologist to obtain patient consent prior to notification. Patient information sheets, consent forms and a copy of this protocol will be made available on the ARC Epidemiology Unit's and the BSR's website or directly from the BSR. Receipt of notification would then act as the initiating event for the collection of the baseline data, recruitment of comparison subjects and all necessary follow up.

Follow–up

Patients are followed up via questionnaires to the rheumatologist on a 6 monthly basis for three years and annually for two years. Patients are also sent a questionnaire and diary directly to their homes on a 6 monthly basis for three years. All patients are flagged with the Office for National Statistics (ONS) for malignancy and mortality.

**C7. Give details of any clinical intervention(s) or procedure(s) to be received by research participants over and above those which would normally be considered a part of routine clinical care.** *(These include uses of medicinal products or devices, other medical treatments or assessments, mental health interventions, imaging investigations and taking samples of human biological material.)*
*(Populated from A12)*

| **Additional Intervention** | **Average number per patient** | | **Average time taken** (mins/hours/days) | **Details of additional intervention or procedure, who will undertake it, and what training they have received.** |
|---|---|---|---|---|
| | Routine Care | Research | | |
| | | | | |

**C8. Give details of any non−clinical research−related intervention(s) or procedure(s).** *(These include interviews, non−clinical observations and use of questionnaires.)*
*(Populated from A13)*

| Additional Intervention | Average number per patient | Average time taken (mins/hours/days) | Details of additional intervention or procedure, who will undertake it, and what training they have received. |
|---|---|---|---|
| Other Questionnaire | 9 | 15 | Questionnaires are sent out directly to the rheumatolgist /nurse on a 6 monthly basis for three years and then annually for two years to capture any changes in therapy, disease activity and adverse events |
| Postal questionnaire to home | 9 | 15 | Patients are sent a questionnaire which measures functional activity (HAQ) and health assessment (SF−36)along with a diary to record hospitalisations, new drugs and referrals on a 6 monthly basis for three years |

**C9a. Give the name of the research site for which the PI is responsible:** *(Please give the name only. Further details of locations should be given in C10. The name of the site is normally the name of the acute NHS Trust, GP practice or other organisation responsible for the care of research participants. In some cases it may be an individual unit, private practice or consortium – see the guidance notes. Each GP practice is a separate site unless a formal consortium/network is in place.)*

**If you wish to add further information about the definition of the site, please do so below:**

**C9b. Give the name of the NHS or other organisation with which the PI holds the necessary contract (substantive or honorary) to undertake the research at this site:**

**C9c. For NHS sites, give the name and contact details of the Research Governance contact for the research site at the care organisation or consortium:**

Title:
Forename/Initials:
Surname:
Address:

Telephone:
Fax:

Postcode:
E−mail:

**C9d. For non−NHS sites, give details of the arrangements for the management and monitoring of the research at this site:**

**C10. Specify all locations or departments at which research procedures will be conducted at this site.**
*Include details of any centres at other NHS care organisations where potential participants may be seen and referred for inclusion in the research at this site. Give details of any research procedures to be carried out off site, for example in participants' homes.*

**C11. How many research participants/samples is it anticipated will be recruited/obtained from this organisation in total?**

**C12a. Give details of who will be responsible for obtaining informed consent locally, their qualifications and relevant expertise and training in obtaining consent for research purposes:**

**C13a. What arrangements have been made for participants who might not adequately understand verbal explanations or written information given in English, or who have special communication needs?** *(e.g. translation, use of interpreters etc.) (Populated from A29)*

As the questionnaires are completed as part of routine clinical practice, arrangements are made at a local level for this if necessary.

**C13b. What local arrangements have been made to meet these requirements (where applicable)?**

☐ Not Applicable

**C14. In addition to informing the GP (if required), what arrangements have been made to inform those responsible for the care of the research participants in the host care organisation of their involvement in the research?**

**C15. Are the facilities and staffing available locally adequate to perform any necessary procedures or interventions required for the study, and to deal with any unforeseen consequences of these?***(This should include consideration of procedures and interventions in both control and intervention arms of a study.)*

◉ Yes ○ No

*If Yes, give the information necessary to justify your answer. If No, indicate what arrangements are being made to deal with the situation:*
grhtykuykiuyuthytytyrtrgtrg

**C16a. Give brief details of a contact point where participants may obtain further information about the study.**

~~frweffefefcefr~~

**C16b. What is the contact point for potential complaints by research participants?**

**C16c. Is there a local source where potential participants can obtain independent information about being involved in a research study?***See guidance notes.*

**C16d. Please specify the headed paper to be used for the participant information sheet.**

**C17. If any extra support might be required by research participants as a result of their participation, what local arrangements are being made to provide this?**

## PART C: Declaration

– The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.

– I undertake to abide by the ethical principles underpinning the Declaration of Helsinki and good practice guidelines on proper conduct of research.

– If the research is approved I undertake to adhere to the study protocol, the terms of the full application of which the main REC has given a favourable opinion and any conditions set out by the main REC in giving its favourable opinion.

– I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to security and confidentiality of patient or other personal data, including the need to register when necessary with the appropriate Data Protection Controller.

– I understand that research records/data may be subject to inspection for audit purposes if required in future.

– I understand that personal data about me as a researcher in this application will be held by the relevant RECs and their operational managers and that this will be managed according to the principles established in the Data Protection Act.

– I understand that the information contained in this application, any supporting documentation and all correspondence with Research Ethics Committees relating to the application will be subject to the provisions of the Freedom of Information Acts. The information may be disclosed in response to a request under the Acts except where statutory exemptions apply.

**Signature of the local Principal Investigator *** .....

Date: (dd/mm/yyyy)

Print Name:

** The Chief Investigator should sign where s/he is also the local Principal Investigator for this research site.*

***PART C IS NOW COMPLETE AND SHOULD BE SUBMITTED** to the NHS Research Ethics Committee responsible for the site–specific assessment.*