NHS Research Ethics Committee
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):
Establishment of a UK Evans' Syndrome Registry

Name of NHS research ethics committee to which application for ethical review is being made:

Project Reference number from above REC: 04/MRE02/49
Submission Date: 15/07/2004

PART A

A1. Title of Research

Full title: Establishment of a UK Evans' Syndrome Registry and molecular investigation of potential causative factors

Key words: Evans' syndrome, incidence, prevalence, pathophysiology, single nucleotide polymorphisms, disease associations

A2. Chief Investigator

Title: Dr First Name/Initials: Drew Last Name: Provan
Post: Senior Lecturer in Haematology
Qualifications: BSc (Hons) MBChB MD FRCP FRCPath
Organisation: Barts and The London
Address: Department of Haematology
The Royal London Hospital
London
Postcode: E1 1BB
Email: a.b.provan@qmul.ac.uk
Telephone: 020-7377-7178
Fax: 020-7377-7016

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

A3. Proposed Study Dates and Duration

Start date: 01/09/2004

End date: 01/09/2014

Duration Years 9 Months

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

If other, give details:

Establishment of a disease registry for a rare blood disorder

A5. Tick the box if your research:

- ☐ involves testing a medicinal product
- ☐ involves investigating a medical device
- ☐ involves additional radiation above that required for clinical care
- ☐ involves using stored samples of human biological material (e.g. blood, tissue)
- ☒ involves taking new samples of human biological material
- ☐ involves only patient records or data, with no direct patient contact
- ☐ involves prisoners or others in custodial care
- ☐ involves adults with incapacity
- ☐ has the primary aim of being educational (eg student research, a project necessary for a postgraduate degree or diploma, other than an MD or PhD)

A6. Do you consider that this research falls within the category where there is no local investigator?

YES ☑ NO ☐

If yes, please justify:

The principal site for the Registry and investigation is The Royal London Hospital. Most samples and information will come from other Trusts but they will not be investigators as such. I will, however, require them to obtain informed consent from their patients before submitting information for the Registry.

Advice can be found in the Guidance Notes on this topic. Some studies do not require further consideration of site-specific issues by NHS Research Ethics Committees, but will still require approval to proceed from the host organisation(s).

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

What is the incidence, prevalence and natural history of Evans' Syndrome?

Evans' Syndrome is an uncommon autoimmune disorder characterised by autoantibodies that react with red cells and platelets. The epidemiology of Evans' has not been studied and this registry would be the first of its kind worldwide.

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

Could genetic markers be used to predict disease severity, type (acute or chronic), or responses to treatment?

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.)*

The Royal London is the main UK centre for autoimmune haematological disease. In the past 2 years we have set up 2 MREC-approved registries: one for adult ITP (an autoimmune platelet disorder) and another for an inherited platelet disorder. Evans' Syndrome is very uncommon and its clinical behaviour is not well characterised. Treatment is often required to stop bleeding or correct anaemia but the therapies available are not very effective. In order to manage patients better and allow them to live normal lives we need to understand more about the disease e.g. what triggers the disease, how does it behave clinically, when is treatment needed and which treatment should be used? None of this information is available because individual hospitals have so few patients with the disorder that these data are difficult to acquire. In order to collect adequate data we need to involve many centres and a UK-based approach would seem most sensible.

In fact, it is very likely that an Intercontinental approach will be required in order to generate sufficient numbers of participants.

We know that this disease is autoimmune and the patients' immune systems are making antibodies against their own red cells and platelets. However, we have no idea how this starts. From diseases like rheumatoid arthritis (also an autoimmune disease) genetic factors clearly play a role and the same is likely to be true for Evans' syndrome. We would like to assess the presence of changes within immune system genes (Single Nucleotide Polymorphisms, or SNPs) in patients with Evans' Syndrome and correlate these with clinical parameters including responses to treatments. It is possible that possession of a particular genetic background may predict which patients will have severe disease, or the polymorphisms may predict response to specific therapies.

A10. Give a brief synopsis/summary of methods and overview of the planned research. This should include a brief description of how prospective research participants and concerned communities (not necessarily geographical) from which they are drawn have been consulted over the design and details of the research. *(Where appropriate a flow chart or diagram should be submitted separately. It should be clear exactly what will happen to the research participant, how many times and in what order.)*

Hypothesis
Single nucleotide polymorphisms (SNPs) may play a role in the pathogenesis of Evans' syndrome. Specific SNPs may be useful markers of severity, chronicity, responses to therapy and overall disease outcome in patients with Evans' syndrome. SNP studies may enhance our understanding of the cause and pathology of autoimmune disease and potentially may help identify new targets for therapeutic intervention. This is a population study looking at potential genetic associations between possession of particular genetic polymorphisms and disease behaviour. Similar studies have been carried out in other autoimmune disorders generating very useful data in terms of associations.

Study end points
Obtaining SNP profiles (phase I and phase II) for 300-500 patients (childhood and adult) with Evans' syndrome and correlation analysis with clinical parameters.

Eligibility
Prospective and retrospective, childhood and adult patients with Evans' syndrome. Informed consent required.

Design
UK Trusts, once they receive LREC approval for the study would obtain informed consent from patients with Evans syndrome, complete a short proforma and send this with one 10ml EDTA sample (5ml in children) to Dr Provan at The Royal London Hospital. No further blood samples are required. Subjects would be identified using a computer-generated study number and their data entered into a purpose-built Evans' Registry database at The Royal London. DNA would be extracted from the blood sample and stored at -20C until required for SNP analysis.SNP assays have already been established by our laboratory since we are conducting 2 very similar MREC-approved registries for other uncommon autoimmune diseases. The methodology used would be identical. We have chosen SNPs from genes involved in the regulation of the immune system.SNPs will be analysed using polymerase chain reaction (SNAPshot) methodology which is a very standard technique.

The genetic (SNP) study will be carried out in two phases:
Phase I SNPs
Those chosen include: Cytokines IL-1, IL-2, IL-4, IL-4R, IL-6, IL-10 (x 3), IFN-g, TNF-a, TGF-b (x 2), Fcg receptors FcgRII & III, NRAMP-1.

Phase II SNPs:
Cytokines: IL-5, IL-8, IL-8RA, IL-8RB, IL-13, IL-15, M-CSF, GM-CSF, G-CSF; Chemokines: CCR2, CCR5, SDF1, RANTES, MIF; Apoptosis genes: CASP8, CD95, CD95L, BCL2; T cell signalling: CTLA4; Others: KIR, HLA.

SNP data will be entered into the database and analysed using Dendrite software (Dendrite Clinical Systems Ltd, Henley-on-Thames, Oxfordshire) and correlations between SNP profile and clinical parameters determined.

Consultations to date
I have discussed Evans' Syndrome with haematology colleagues worldwide and we all agree that an Evans' Syndrome Registry would be of major value. The Evans' Syndrome Patients' Association (PISCES) are very keen for us to establish such a registry since current investigation and management of Evans' Syndrome are very unsatisfactory, largely because the disease has never been studied in detail by an group.

Cantagrel, A. et al (1999) Interleukin-1beta, interleukin-1 receptor antagonist, interleukin-4, and interleukin-10 gene polymorphisms: relationship to occurrence and severity of rheumatoid arthritis. Arthritis Rheum, 42, 1093-100; Fishman, D. et al. (1998) The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J Clin Invest, 102, 1369-76; Hackstein, H. et al. (1999) The IL-4 receptor alpha-chain variant Q576R is strongly associated with decreased kidney allograft survival. Tissue Antigens, 54, 471-7

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

This type of registry normally runs for 5-10 years or more. After initial registration there will be simple questionnaires sent to clinicians 6 monthly to document patients' current status and treatment.

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

None

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

None

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

If we can identify risk markers or predictors of severity/chronicity this would have potential benefit for participants. However, this is essentially a disease-association study and the direct benefits to individuals will not be seen for some time.

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

None

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

Identification
Patients known to have Evans' syndrome will be involved in the study. Newly diagnosed patients will also be eligible. These patients are generally well known to haematologists through their outpatient clinics.

Approached and recruited
After obtaining LREC approval haematologists in Trusts throughout the UK will be able to ask patients with Evans' syndrome if they would like to take part in the Registry. After reading the patient information sheet, the patient will be asked if s/he wishes to take part in the study. If they agree to take part in the Registry they will then be asked to sign the consent form, and a 10ml blood sample (5ml in children) will be taken (at the same time as their routine blood tests to avoid additional venepuncture). This sample will be sent to The Royal London along with the completed Clinician Proforma.

A21. Will research participants be recruited via advertisement?

Give details: YES ☑ NO ☐

We would like to advertise the Registry to UK Haematologists through the British Society for Haematology newsletter (quarterly) and via the Evans' Syndrome patient association (PISCES) website.

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.)*

Patients with Evans' syndrome (autoimmune haemolytic anaemia and thrombocytopenia) in the absence of any other underlying diseases). The disorder probably affects children more than adults and we would like to involve both paediatric and adult participants in the Registry. This would provide a more accurate overview of the disease and also, since the disorder is rare, a greater number of participants.

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

Subjects who do not wish to take part.
Individuals where there is underlying disease likely to produce haemolytic anaemia and thrombocytopenia.
Any patient in whom Evans' disease seems unlikely.

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 suffering from 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:

The disorder affects all ages, and probably children more than adults although such data are not available. The study would be skewed if only adults are involved. Therefore, we would very much like to include paediatric patients and the paediatricians we have discussed this with are keen to be included in the study.

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

What steps will you take to find out? YES ☐ NO ☐ Not Known ☑

This is very unlikely since there are no ongoing studies that I know of involving Evans' Syndrome.

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

YES ☑ NO ☐

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 the arrangements to be made for obtaining consent from a legal representative.

Consent may be obtained by haematologists (senior or junior) who are familiar with the aims of the Registry and whose Trust has LREC approval.

Research nurses involved in clinical trials should be allowed to obtain consent providing their Trust has LREC approval.

For paediatric patients, the clinician or nurse would be required to explain the nature of the study to the parents, and if they are happy for their child to take part then the child could be registered.

No vulnerable groups (apart from standard paediatric patients) will be involved.

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 ☐

Attach a copy of the consent form 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?

There will be no pressure to take part; unlimited time available.

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

This is a problem mainly for London, Birmingham and other centres with a wide ethnic mix. Advocates (translators or interpreters) would be required in order to explain the process. If language is a problem e.g. no interpreters available then such a patient could not feasibly be expected to take part. However, most hospitals with significant numbers of patients for whom English is not the first language generally have good patient advocacy services and we would hope this should enable such patients to take part.

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?

There is a website where information (fully anonymised and simplified) will be available. Data will also be presented at meetings (again, anonymised) and clinicians will be informed about the progress with the study and will be able to pass this information to their participating patients.

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

YES ☑ NO ☐

Give details:

There is an Evans ' Syndrome Support Group (PISCES) and this registry is fully endorsed by them.

A32. Will the research participant's General Practitioner be informed that they are taking part in the study?

YES ☑ NO ☐

Enclose a copy of the information sheet/letter for the GP with a version number and date.

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

YES ☑ NO ☐

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 ☑

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

YES ☐ NO ☑

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?

Trusts will be given indemnity after obtaining LREC approval. The principal site where the study is being performed (The Royal London) will obtain indemnity through the Barts and the London R & D Office.

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?

This is a demographic/epidemiology registry study and does not involve procedures or drugs and will be covered by the Trust Indemnity scheme.

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 the research be made available to research participants and communities from which they are drawn?

Through Newsletters, presentations and meetings including support groups and via the Web (dedicated site for Evans' Syndrome)

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, email, or computer networks
- ☐ Sharing of data with other organisations
- ☐ Export of data outside the European Union
- ☒ Use of personal addresses, postcodes, faxes, emails 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 computer

Further details:

Data will be submitted in paper form (proformas) to Dr Provan. The information will be entered into a specific database by our Registry Coordinator. Evans' Syndrome Registry numbers will be allocated by the computer and subjects will be identified using this number. Names and addresses will be not be used (we do not seek names or other identifiers on our proforma - see Clinician Proforma), hospital numbers will be kept separately with password control, as aids for identifying patients later when we wish to look at outcomes over a given time period.

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

Data will be semi-anonymised as described in the previous section. We will require a method for identifying individuals in order to carry out this longitudinal study but we will generally use the computer-generated Registry number most of the time. Data will be password protected. We may need to use the case notes number for communications with referring clinicians when we require follow-up information (in order that they can determine which patient we need follow-up data from).

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

Data will be analysed at The Royal London. We have a Trust-wide site licence for Dendrite (this software currently analyses data for Cardiac Surgery and several other Directorates in the Trust). Data (minus identifiers) will be analysed by the software and associations determined and plotted by the statistical software.

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

Dr Drew Provan, Department of Haematology, The Royal London Hospital.

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

Dr Provan, Professor Newland (Head of Department, Haematology, Barts and The London), our research nurse, our data manager. Because we are assessing responses to specific therapeutic agents some selected anonymised data may be shared with industry colleagues.

A44. For how long will data from the study be stored? 10 Years Months

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

Dr Provan's computer, Royal London Hospital (removable drive, password protected system involved).

A45. 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

If other, give details:

This Registry precisely mirrors our other 2 registries which were recently peer-reviewed.

If you are not in possession of any referees' or other scientific critique reports relevant to your proposed study, justify and describe the review process and outcome. If review has been undertaken but not seen by the researcher, give the details of the body which has undertaken the review:

A copy of any referees' comments or other scientific critique reports relevant to the proposed research must be enclosed with the application form.

A46. Has similar research on this topic been done before?

YES ☐ NO ☑

A47. Have all existing sources of evidence, especially systematic reviews, been fully considered?

YES ☑ NO ☐

Please give details of search strategy used:

This is a very small field and I know all researchers interested in this area of haematology. There are a few scattered publications related to Evans' Syndrome but nothing substantive to date.

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

To assess incidence, prevalence and natural history of Evans' Syndrome in children and adults

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

To determine whether SNPs (genetic polymorphisms) are of value in determining outcomes or responses to treatment.

A50. How many participants will be recruited? How many of these participants will be in a control group?

As many UK patients with Evans' Syndrome as possible. Hopefully 300-500 participants but since the incidence is not known I am uncertain whether we will achieve this number using UK patients only. A similar number of controls will be used.

A51. Has the size of the study been informed by a formal statistical power calculation?

YES ☐ NO ☑

A52. Has a statistician given an opinion about the statistical aspects of the research?

YES ☑ NO ☐

Give the name and contact details:

Our in-house statistician has been consulted. There are few data concerning Evans' syndrome so we cannot put an exact number of cases needed for robust statistical analysis.

Give a brief summary of advice offered and attach a copy of the comments if available:

Enclose a copy of comments. If the comments are not available then please enclose a summary of the opinion.

A53. Describe the statistical methods and/or other relevant methodological approaches (e.g. for qualitative research) to be used in the analysis of the results. Give details of the methods of randomisation process to be used if applicable:

This is a fairly simple Registry study and these type of statistics are not relevant to the study.

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

- ☑ UK
- ☐ Other States in the European Union
- ☐ Other States in the European Economic Area
- ☑ Other

Give details:

We would eventually like to collaborate with our European and US colleagues since the disorder is uncommon and we may need to join up with other countries in order to accrue sufficient participants. If the true incidence is very low then we will almost certainly need to invite other countries to join the UK Registry.

A55. Has this or a similar application been previously rejected by a Research Ethics Committee in the UK, the European Union or in 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 that 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 Community and/or Primary Care Trusts	
☐	NHS Trusts providing mental healthcare	
☐	NHS Care Trusts	
☐	Social Care Organisations	
☐	Prisons	
☐	Independent hospitals	
☐	Educational establishments	
☐	Independent research units	
☐	Other (give details)	

All UK Hospital Trusts (those dealing with haematology i.e. most hospitals) will be invited to take part. We accept that not all of these will wish to do so but we are keen to involve as many groups as possible.

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

Barts and The London has a robust Research Governance Department and they will be monitoring the research. Full project details have been registered with Barts and The London NHS Trust R&D Department.

Will a data monitoring committee be convened? YES ☐ NO ☑

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

N/A

A58. Has funding for the research been secured? YES ☑ NO ☐

Give details of funding organisation(s), amount secured and duration of funding:

i

Organisation: Evans' Syndrome Association (PISCES Trust)
Address: 11 Burrough Close, Oakwood, Warrington
Postcode: WA3 6QF
UK Contact: Ms Michelle Aspinall
Telephone: 01925-488825 Fax: 01925-488825
Email: piscestrust@hotmail.com
Amount: £ £20,000.00 Duration: 12 months

ii

Organisation:
Address:
Postcode:
UK Contact:
Telephone: Fax:
Email:
Amount: £ Duration: months

iii

Organisation:
Address:
Postcode:
UK Contact:
Telephone: Fax:
Email:
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 ☑ Not yet known ☐

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

YES ☑ NO ☐ Not yet known ☐

Give details of the organisation who will act as the sponsor of the research:

Organisation: Barts and The London NHS Trust
Address: Whitechapel, London
Postcode: E1 1BB
UK Contact: Mr Gerry Leonard
Telephone: 0207-377-2403 Fax:
Email: gerry.leonard@bartsandthelondon.nhs.uk

A copy of documentation indicating that the organisation has accepted the role of sponsor should be enclosed if the sponsor is not the main funder, the Chief Investigator's employer, or an NHS body hosting the research.

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

YES ☐ NO ☑

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

YES ☐ NO ☑

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

YES ☐ NO ☑

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 ☑

A64. Does the Chief Investigator or any other key 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 ☑

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

Applicant's/organisation's own reference number, e.g. R&D (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:	

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

i

Title:	Profess	First Name/Initials:	Adrian C	Last Name:	Newland
Post:	Professor of Haematology, Head of Service				
Qualifications:	MA FRCP FRCPath				
Organisation:	Barts and The London, Queen Mary School of Medicine & Dentistry				
Address:	Department of Haematology The Royal London Hospital London			Telephone: Fax:	020-7377-7180 020-7377-7016
Postcode:	E1 1BB	Email:	a.c.newland@qmul.ac.uk		

ii

Title:		First Name/Initials:		Last Name:	
Post:					
Qualifications:					
Organisation:					
Address:				Telephone: Fax:	
Postcode:		Email:			

iii

Title:		First Name/Initials:		Last Name:	
Post:					
Qualifications:					
Organisation:					
Address:				Telephone: Fax:	
Postcode:		Email:			

iv

Title:		First Name/Initials:		Last Name:	
Post:					
Qualifications:					
Organisation:					
Address:				Telephone: Fax:	
Postcode:		Email:			

v

Title:		First Name/Initials:		Last Name:	
Post:					
Qualifications:					
Organisation:					
Address:				Telephone: Fax:	
Postcode:		Email:			

If there are more than 5 collaborators, please enter at end of section or attach a further sheet.

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?

N/A

Summary of Ethical Issues

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

Genetic data are involved in this study but this is a population-based disease-association study. For this reason the genetics aspects should not pose a problem. As outlined earlier, as a population-based study, individual identifiers will never be published and anonymity will be maintained. If patients wish more detailed information regarding the genetic aspects of the study these will be addressed either by Dr Provan or our Directorate's genetic counsellor. For a similar registry (The UK Adult ITP Registry) Dr Provan has written in detail about the genetic aspects in regular patient newsletters and one several annual patient conferences.

A69. Do you need to add further information about certain questions in Part A?

YES ☐ NO ☑

PART B: Section 5 - Use of newly obtained Human Biological Materials

1. What samples will be collected and/or analysed, and by whom will they be collected?

10ml EDTA on one occasion (5ml for children) per participant. This will be used for DNA extraction. The DNA will be housed in our Department of Experimental Haematology and will be looked after by a senior postdoctoral fellow. In view of the Human Tissue Act our Trust is considering establishing a central core facility for storage of such material with a designated curator so we can maintain samples in accordance with new legislation. If this is set up we will house our samples in this facility.

2. Are samples taken solely for research purposes (or are they a by-product of those taken primarily for clinical purposes i.e. surplus to clinical requirements)?

This 10ml (or 5ml for children) EDTA sample we require will be taken for research only; we will not use any unused diagnostic specimens.

3. How will samples be labelled/identified?

Indicate if samples can be considered to be "identified", "coded", "de-identified", "anonymised" or "anonymous", and at what stage identifiers are removed. (See Guidance Notes for definitions.)

We will allocate a specific Registry number to each sample and this will be the only identifier used.

4. Give details of where the sample(s) will be stored, for how long, who will have access and of the custodial arrangements.

See above. Samples will be stored for the duration of the study.

5. Will the research participant retain any rights to the sample(s)?

YES ☐ NO ☑

6. Is it known how the samples will be used in the future?

YES ☐ NO ☐

Give details and indicate if consent will be obtained for the future use of samples:

They will be used solely for the purposes stated. We have no intention of supplying the DNA to third parties.

7. Does the research involve the analysis or use of genetic material from human biological materials?

YES ☑ NO ☐

8. Would it be possible to link the results of any genetic analysis back to individuals?

YES ☑ NO ☐

9. Is it intended to link the results of any genetic analysis back to individuals?

YES ☑ NO ☐

Give details of what support or counselling service will be available to individuals:

Because this is a longitudinal study we need to know what happens to individuals over time , on treatment, off treatment etc. We therefore need some mechanism of correlating specific genetic markers with disease outcome. However, the study is a population-based disease-association study and we are not expecting specific genetic markers to be applied to individuals. In addition we are only analysing polymorphisms (not mutations) and so genetic counselling should not be required. Dr Provan has a degree in molecular genetics and is happy to explain the genetics to any participant or clinician. We also have an divisional genetic counsellor who is available for genetic counselling should this be required.

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 without unagreed deviation and to comply with any conditions set out in the letter sent by the NHS Research Ethics Committee notifying me of this.
- I undertake to inform the NHS Research Ethics Committee of any changes in the protocol, and to submit annual 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 Research Ethics Committee and its operational managers, and that this will be managed according to the principles established in the Data Protection Act.

Signature of the Chief Investigator: .....

Date:

Print Name:

1. Do you need to add further information about certain questions in Part B?

YES ☐ NO ☐

ENSURE THAT YOU COMPLETE AND SIGN THE FORM, AND ENCLOSE ALL RELEVANT ADDITIONAL DOCUMENTS.

NHS Research Ethics Committee
APPLICATION FORM
PART C: SITE-SPECIFIC ASSESSMENT

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

Part C should be completed and sent with relevant enclosures to each NHS Research Ethics Committee or Research & Development (R&D) department which needs to consider site-specific issues. Consult the application procedure on the COREC website.

The data in this box is populated from Part A.

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

Project Reference number from above REC: 04/MRE02/49

Name of site NHS REC (or R&D department) undertaking site-specific assessment:

Site NHS REC (or R&D Department) Identifier:

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

C1. Title of Research. *(Populated from A1)*

Full title: Establishment of a UK Evans' Syndrome Registry and molecular investigation of potential causative factors

Key words: Evans' syndrome, incidence, prevalence, pathophysiology, single nucleotide polymorphisms, disease associations

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

Title: First Name/Initials: Last Name:

Post:

Qualifications:

Organisation

Address:

Postcode:

Email:

Telephone:

Fax:

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

C3. Indicate the number of trials/projects within the organisation that the local Principal Investigator has been involved with in the previous 12 months: 4

How many are still current (active or recruiting)? 4

Give details of other members of the local research team responsible to the local Principal Investigator

i Title: Dr First Name/Initials Ulrika Last Name: Johansson
Position: Post-doctoral scientist
Qualifications: BSc PhD
Role in the research team: Scientist performing SNP analyses

ii Title: Mrs First Name/Initials Deborah Last Name: Kenny
Position: Grade H Sister
Qualifications: RGN
Role in the research team: Specialist nurse running ITP trials and helping with Registries

iii Title: First Name/Initials Last Name:
Position:
Qualifications:
Role in the research team:

If there are more members of the local research team, details should be provided at question C18 or on an attached sheet.

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

Title: Dr First Name/Initials: Drew Last Name: Provan
Post: Senior Lecturer in Haematology
Qualifications: BSc (Hons) MBChB MD FRCP FRCPath
Organisation: Barts and The London
Address: Department of Haematology
The Royal London Hospital
London
Postcode: E1 1BB
Email: a.b.provan@qmul.ac.uk
Telephone: 020-7377-7178
Fax: 020-7377-7016

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

Applicant's/organisation's own reference number, e.g. R&D (*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:

C6. Give a brief synopsis/summary of methods and overview of the planned research. This should include a brief description of how prospective research participants and concerned communities (not necessarily geographical) from which they are drawn have been consulted over the design and details of the research. *(Where appropriate a flow chart or diagram should be submitted separately. It should be clear exactly what will happen to the research participant, how many times and in what order.) (Populated from A10.)*

Hypothesis
Single nucleotide polymorphisms (SNPs) may play a role in the pathogenesis of Evans' syndrome. Specific SNPs may be useful markers of severity, chronicity, responses to therapy and overall disease outcome in patients with Evans' syndrome. SNP studies may enhance our understanding of the cause and pathology of autoimmune disease and potentially may help identify new targets for therapeutic intervention. This is a population study looking at potential genetic associations between possession of particular genetic polymorphisms and disease behaviour. Similar studies have been carried out in other autoimmune disorders generating very useful data in terms of associations.

Study end points
Obtaining SNP profiles (phase I and phase II) for 300-500 patients (childhood and adult) with Evans' syndrome and correlation analysis with clinical parameters.

Eligibility
Prospective and retrospective, childhood and adult patients with Evans' syndrome. Informed consent required.

Design
UK Trusts, once they receive LREC approval for the study would obtain informed consent from patients with Evans syndrome, complete a short proforma and send this with one 10ml EDTA sample (5ml in children) to Dr Provan at The Royal London Hospital. No further blood samples are required. Subjects would be identified using a computer-generated study number and their data entered into a purpose-built Evans' Registry database at The Royal London. DNA would be extracted from the blood sample and stored at -20C until required for SNP analysis.SNP assays have already been established by our laboratory since we are conducting 2 very similar MREC-approved registries for other uncommon autoimmune diseases. The methodology used would be identical. We have chosen SNPs from genes involved in the regulation of the immune system.SNPs will be analysed using polymerase chain reaction (SNAPshot) methodology which is a very standard technique.

The genetic (SNP) study will be carried out in two phases:
Phase I SNPs
Those chosen include: Cytokines IL-1, IL-2, IL-4, IL-4R, IL-6, IL-10 (x 3), IFN-g, TNF-a, TGF-b (x 2),
Fcg receptors FcgRII & III, NRAMP-1.

Phase II SNPs:
Cytokines: IL-5, IL-8, IL-8RA, IL-8RB, IL-13, IL-15, M-CSF, GM-CSF, G-CSF; Chemokines: CCR2, CCR5, SDF1, RANTES, MIF; Apoptosis genes: CASP8, CD95, CD95L, BCL2; T cell signalling: CTLA4; Others: KIR, HLA.

SNP data will be entered into the database and analysed using Dendrite software (Dendrite Clinical Systems Ltd, Henley-on-Thames, Oxfordshire) and correlations between SNP profile and clinical parameters determined.

Consultations to date
I have discussed Evans' Syndrome with haematology colleagues worldwide and we all agree that an Evans' Syndrome Registry would be of major value. The Evans' Syndrome Patients' Association (PISCES) are very keen for us to establish such a registry since current investigation and management of Evans' Syndrome are very unsatisfactory, largely because the disease has never been studied in detail by an group.

Cantagrel, A. et al (1999) Interleukin-1beta, interleukin-1 receptor antagonist, interleukin-4, and interleukin-10 gene polymorphisms: relationship to occurrence and severity of rheumatoid arthritis. Arthritis Rheum, 42, 1093-100;
Fishman, D. et al. (1998) The effect of novel polymorphisms in the interleukin-6 (IL-6) gene on IL-6 transcription and plasma IL-6 levels, and an association with systemic-onset juvenile chronic arthritis. J Clin Invest, 102, 1369-76;
Hackstein, H. et al. (1999) The IL-4 receptor alpha-chain variant Q576R is strongly associated with decreased kidney allograft survival. Tissue Antigens, 54, 471-7

C9. Name of NHS or other organisation where the research will take place.

C10. Specify the location(s)/department(s) within the NHS or other organisation where the research will take place.

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

C12. 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:

C13. What local arrangements have been made for participants who might not adequately understand verbal explanations or written information given in English? *(e.g. translation, use of interpreters etc.)*

C14. What arrangements have been made to inform those responsible for the care of the research participants 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 ☐

Indicate what arrangements are being made:

C16. Give details of a contact point where participants may obtain further information about the study.

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

C17. If there is no Principal Investigator at local level , is there a local individual who is undertaking a task relating to the research?

YES ☐ NO ☐ Not Applicable ☐

Give details:

C18. Do you need to add further information about certain questions in Part C?

YES ☐ NO ☐

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 current proper conduct of research.
- If the research is approved I undertake to adhere to the study protocol without unagreed deviation and to comply with any conditions set out in the letter sent by the NHS Research Ethics Committee notifying me of this.
- I undertake to inform the NHS Research Ethics Committee of any changes in the protocol, and to submit annual 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 Research Ethics Committee and its operational managers, and that this will be managed according to the principles established in the Data Protection Act.

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

Date:

Print Name:

** The Chief Investigator should sign where there is no local Principal Investigator for the research locality.*

PART C IS NOW COMPLETE AND SHOULD BE SUBMITTED to the NHS Research Ethics Committee or NHS organisation conducting site-specific assessment