

APPLICANT'S CHECKLIST

All studies except clinical trials of investigational medicinal products

REC Ref:	07/H0718/57
Short Title of Study:	United Kingdom Adult ITP Registry
CI Name:	Dr. Drew Provan
Sponsor:	Barts and the London NHS Trust

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 – UKITP Cover Letter	<input checked="" type="radio"/> Yes <input type="radio"/> No	03/07/2007		
NHS REC Application Form, Parts A&B – UKITP Parts A&B	Mandatory	03/07/2007	No Version	
Site-Specific Information Form (for SSA) – UKITP Part SSI Form	<input checked="" type="radio"/> Yes <input type="radio"/> No	03/07/2007	No Version	
Research protocol or project proposal (6 copies) – UKITP Study Protocol & UKITP Analysis Plan	Mandatory	03/07/2007	1.1	
Summary C.V. for Chief Investigator (CI) – UKITP PI CV-Provan	Mandatory	26/03/2007		
Summary C.V. for supervisor (student research) – UKITP Primary Supervisor CV-Sanderson	<input checked="" type="radio"/> Yes <input type="radio"/> No	03/02/2007		
Research participant information sheet (PIS) – UKITP Prospective Participant Overview	<input checked="" type="radio"/> Yes <input type="radio"/> No	03/07/2007	2.0	
Research participant information sheet (PIS) – UKITP Past Patient Overview	<input checked="" type="radio"/> Yes <input type="radio"/> No	03/07/2007	1.6	
Research participant consent form – UKITP Study Informed Consent Agreement	<input checked="" type="radio"/> Yes <input type="radio"/> No	03/07/2007	1.5	
Research participant consent form – UKITP Subsequent Tissue Usage Informed Consent Agreement	<input checked="" type="radio"/> Yes <input type="radio"/> No	03/07/2007	1.1	
Letters of invitation to participants	<input type="radio"/> Yes <input checked="" type="radio"/> No			
GP/Consultant information sheets or letters – UKITP Haematologist Overview	<input checked="" type="radio"/> Yes <input type="radio"/> No	03/07/2007	1.4	
Statement of indemnity arrangements – UKITP BLT Sponsorship Letter	<input checked="" type="radio"/> Yes <input type="radio"/> No	15/05/2007		
Letter from sponsor – UKITP BLT Sponsorship Letter	<input checked="" type="radio"/> Yes <input type="radio"/> No	15/05/2007		
Letter from statistician – UKITP Statistical Review-Colopy	<input checked="" type="radio"/> Yes <input type="radio"/> No	08/03/2007		
Letter from funder	<input type="radio"/> Yes <input checked="" type="radio"/> No			
Referees' or other scientific critique report – UKITP R&D Approval	<input checked="" type="radio"/> Yes <input type="radio"/> No	20/06/2007		

Referees' or other scientific critique report – UKITP ICMS Internal Peer Review	<input checked="" type="radio"/> Yes <input type="radio"/> No	25/04/2007		
Referees' or other scientific critique report – UKITP Internal Peer Review–MacCallum	<input checked="" type="radio"/> Yes <input type="radio"/> No	04/04/2007		
Referees' or other scientific critique report – UKITP Internal Peer Review–Dokal	<input checked="" type="radio"/> Yes <input type="radio"/> No	16/04/2007		
Summary, synopsis or diagram (flowchart) of protocol in non–technical language	<input type="radio"/> Yes <input checked="" type="radio"/> No			
Interview schedules or topic guides for participants	<input type="radio"/> Yes <input checked="" type="radio"/> No			
Validated questionnaire	<input type="radio"/> Yes <input checked="" type="radio"/> No			
Non–validated questionnaire	<input type="radio"/> Yes <input checked="" type="radio"/> 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.	<input type="radio"/> Yes <input checked="" type="radio"/> No			
UKITP Initial Information Sheet	<input checked="" type="radio"/> Yes <input type="radio"/> No	03/07/2007	1.4	
UKITP Six–Month Information Sheet	<input checked="" type="radio"/> Yes <input type="radio"/> No	03/07/2007	1.1	
UKITP Annual Information Sheet	<input checked="" type="radio"/> Yes <input type="radio"/> No	03/07/2007	1.1	

WELCOME TO THE NHS RESEARCH ETHICS COMMITTEE APPLICATION FORM

An application form specific to your project will be created from the answers you give to the following questions.

1. Is your project an audit or service evaluation?

Yes No

2. Select one research category from the list below:

- Clinical trials of investigational medicinal products
 Clinical investigations or other studies of medical devices
 Other clinical trial or clinical investigation
 Research administering questionnaires/interviews for quantitative analysis, or using mixed quantitative/qualitative methodology
 Research involving qualitative methods only
 Research limited to working with human tissue samples and/or data
 Research tissue bank

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

Other research

2a . Please answer the following questions:

- a) Does the study involve the use of any ionising radiation? Yes No
b) Will you be taking new human tissue samples? Yes No
c) Will you be using existing human tissue samples? Yes No

3. Is your research confined to one site?

Yes No

4. Does your research involve work with prisoners?

Yes No

5. Do you plan to include in this research adults unable to consent for themselves through physical or mental incapacity?

Yes No

6. Is the study, or any part of the study, being undertaken as an educational project?

Yes No

6a. Is the project being undertaken in part fulfilment of a PhD or other doctorate?

Yes No

NHS Research Ethics Committee **Application form for research administering questionnaires/interviews for quantitative analysis or mixed methodology study**

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)

United Kingdom Adult ITP Registry

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

London Research Ethics Committee

Project reference number from above REC: 07/H0718/57

Submission date: 03/07/2007

PART A: Introduction**A1. Title of the research**

Full title: United Kingdom Adult Idiopathic Thrombocytopenic Purpura (ITP) Registry: An Investigation of Disease Progression, Treatment Effectiveness, and Co-morbid Conditions

Key words: Thrombocytopenia
ITP
Adult
PARC

A2. Chief Investigator

Title: Dr.

Forename/Initials: Drew

Surname: Provan

Post: Senior Lecturer in Haematology

Qualifications: BSc MBChB DM FRCP FRCPATH

Organisation: Barts and the London, Queen Mary's School of Medicine and Dentistry

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Fax: (0)20-3246-0351

Mobile: (0)78-9416-2792

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: 01/07/2007

End date: 01/07/2017
 Duration: Years: 10 ; Months: 0

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

Question(s) 5 disabled.

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

Yes No

If No, please justify:

The research conducted under this proposed study would consist of simple data collection from patient medical records and the collection of an extra 10 mL (~2 teaspoonsful) of blood during routine venepuncture at outpatient clinics.

The data templates sent to participants' haematologists would request information that would be collected as part of routine care of patients presenting with idiopathic thrombocytopenic purpura (ITP). This research would, therefore, pose a very low risk of harm or emotional distress among study participants.

While patient identifying details will be stored centrally to prevent duplicate enrollment and ensure accurate participant follow-up, they will not be contained within the primary study database. Instead, each centre and patient will be allocated a unique reference number whose key will only be made available to the chief investigator and study coordinator. This encrypted key will be stored on the chief investigator's personal password-protected NHS computer. All analyses will be conducted via the anonymised database, assuring patient confidentiality.

Local consultant haematologists will alert the study coordinator to potential participants so that recruitment and informed consent can be directed by the chief investigator's team. They will then download consent forms and information sheets from a secure study server and discuss their contents with eligible patients, who will have an additional opportunity to pose questions or concerns with members of the chief investigator's team directly by telephone. Written consent will be taken locally and stored in the patient's notes locally, with a copy forwarded to the study data manager at The Royal London Hospital.

If Yes, an application for SSA should be made for each research site on the Site-Specific Information Form and submitted to the relevant local Research Ethics Committee. Do not apply for SSA at sites other than the lead site until the main 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 R&D office for each NHS care organisation in which research procedures are undertaken. This applies whether or not the research is exempt from SSA. R&D applications in England, Wales and Scotland should be made using the Site-Specific Information Form.

PART A: Section 1

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

The objective of this study is to establish a registry of adult idiopathic thrombocytopenic purpura (ITP) patients in the United Kingdom to uncover information with regard to disease burden and progression, treatment effectiveness, and potentially associated co-morbid conditions.

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

1. To compile an anonymised database of demographic, disease-specific, and co-morbid information on patients representative of the adult ITP population in the United Kingdom
2. To estimate the incidence and prevalence of adult ITP in the United Kingdom
3. To estimate the disease progression of adult ITP
4. To document adult ITP treatment practices in the United Kingdom and to contrast these findings with current guidelines put forward by the British Committee for Standards in Haematology (BCSH)
5. To estimate the effectiveness of currently available treatments for adult ITP
6. To test associations of single nucleotide polymorphisms (SNPs), or base changes within genes representing population variants rather than mutations, with disease severity and responses to treatments among adult ITP patients
7. To compare gene expression patterns between adult patients exhibiting severe and non-severe ITP at diagnosis and adult ITP patients responsive to and non-responsive to prednisolone 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.)*

Background:

ITP is an autoimmune disorder in which the production of autoantibodies to proteins on a patient's platelets results in their premature destruction in the peripheral bloodstream, resulting in a marked reduction in platelet count (Porcelijn and von dem Borne, 1998). ITP affects all ages and both sexes with a slight female preponderance. Clinical consequences include bruising, mucousal bleeding, retinal haemorrhage, nosebleeds, gastrointestinal haemorrhage, and excessive menstrual bleeding.

Pathogenesis of ITP:

As with most autoimmune diseases, the cause of ITP is not known. In children, acute ITP typically follows a trivial viral infection and tends to be transient, requiring no treatment (George, et al., 1996). However, in many adults, the disease is chronic, with only some patients exhibiting spontaneous recovery. We wish to examine DNA and RNA from adult ITP patients in order to determine whether specific SNPs or patterns of gene expression are associated with ITP susceptibility, severity, or resolution among adults.

Treatment:

Treatment of ITP is seldom necessary if the peripheral platelet count is greater than $20-30 \times 10^9/L$, especially if there are few spontaneous bleeding episodes (British Committee for Standards in Haematology, 2003). In adults with symptomatic ITP, conventional treatment comprises one or a combination of the following: (1) corticosteroids (2) intravenous immunoglobulin (IVIg) (3) immunosuppression (e.g. azathioprine) (4) anti-D (5) splenectomy. There have been few good quality trials comparing different treatments in ITP, but it is recognised that treatment response varies greatly to different treatments. The availability of indicators of response e.g. specific polymorphisms within immune response genes, may aid decision-making among this

heterogeneous group of patients.

Disease Registries:

Population-based disease registries are invaluable in the study of rare disorders, as single centre experience is unlikely to yield sufficient data to guide treatment. By using a disease registry, we will be able to collate sufficient demographic and clinical information to allow us to determine the true incidence and likely outcome of as well as the optimal therapy for adult ITP; we will also learn more about the cause and biology of autoimmune diseases in general. Through our involvement with The ITP Support Association, we will be able to keep patients fully informed regarding the outcomes of the study. In addition, registries can provide a useful medium for alerting patients to new therapies, drug trials, and other innovations.

References:

- 1) L. Porcelijn, A. E. von dem Borne, *Baillieres Clinical Haematology* 11, 331–41 (1998)
- 2) J. N. George, et al., *Blood* 88, 3–40 (1996)
- 3) British Committee for Standards in Haematology, *British Journal of Haematology* 120, 574–596 (2003)

A10–1. 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.

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 the Site-Specific Information Form. Do not simply reproduce or refer to the protocol. Further guidance is available in the guidance notes.

Purpose:

This study seeks to uncover information regarding the burden, natural progression, treatment effectiveness, and co-morbidities of adult ITP in the United Kingdom via establishment of a multi-centre disease registry.

Background:

A previous version of this study was submitted to the London Multi-centre Research Ethics Committee (MREC) in 2002 under the title, "Establishment of a UK Registry for Adults with Idiopathic Thrombocytopenic Purpura (ITP) and Investigation into the Role of Cytokine Genes." The proposed study was ethically approved in August 2002 (MREC/02/2/58) and remained active until August 2005, during which time over 600 patients were enrolled.

However, due to unforeseen circumstances resulting in a switch of positions, the chief investigator was forced to limit further investigation and analysis on this cohort at that time. He has since returned to the Royal London Hospital as both a senior clinical lecturer and consultant haematologist and is eager to reinstate the study with minor substantive alterations. He will be aided in this task by a study coordinator, a molecular scientist, and a data manager, full-time positions funded through support from GlaxoSmithKline Inc. and The ITP Support Association.

Design & Methodology:

Recruitment & Consent:

The proposed protocol entails investigations into both prospective and past study participants. Within haematology clinics at collaborating centres, adult patients presenting with low platelet counts ($< 150 \times 10^9$ platelets/L) and exhibiting no evidence of other underlying thrombocytopenic (low-platelet) diseases following a standard ITP workup will be invited to take part in the investigation.

This recruitment process will be directed by the study coordinator. Consent forms and information sheets will be electronically downloaded from the secure study server by local collaborating haematologists, who will discuss their content with study invitees. Potential participants will additionally have the opportunity to discuss questions or concerns with members of the chief investigator's team via telephone. Written consent will be taken and stored at locally, with copies of the agreement forwarded to both the study data manager and the study participant.

Blood Collection & Genetic Testing:

At the time of registration, one blood sample (10 ml, ~2 teaspoonsful) will be drawn during a routinely scheduled venepuncture and mailed to the study coordinator, who will be responsible for its semi-anonymisation via labeling with uniquely allocated participant and centre reference numbers. The sample will then be forwarded to the Molecular Haematology Laboratory at The Royal London Hospital, where its genetic contents will be isolated and stored for subsequent single-nucleotide polymorphism (SNP) and gene expression analysis.

We will use polymerase chain reaction (PCR) technology to amplify DNA regions of genes hypothesised to be linked with ITP and other autoimmune diseases. As illustrated in Table 1, the presence of SNPs within genes coding for IL-1(alpha), IL-2, IL-4, IL-4R, IL-6, IL-8, IL-10, TGF-(beta), TNF-(alpha), IFN-(gamma), Fc(gamma)RII & III, CTLA-4, NRAMP-1, CTLA-4, and GAL-2 will be recorded and assessed for their ability to predict disease severity and patient response to treatments.

Table 1: Genes for SNP Testing

Genes	Citation
IL-1(alpha)	McDowell et al., 1995
IL-2	John et al., 1998
IL-4	Cantagrel et al., 1999
IL-4R	Hackstein et al., 1999
IL-6	Fishman et al., 1998
	Olomolaiye et al., 1998
IL-8	Bornscheuer et al., 1999
IL-10 (x 3)	Turner et al., 1997
TGF-(beta) (x 2)	Lympany et al., 1998
TNF-(alpha)	Wilson et al., 1997
IFN-(gamma)	Siegmund et al., 1998
Fc(gamma)RII & III	Jiang et al., 2000
NRAMP-1	Singal et al., 2000
CTLA-4	Heward et al., 1999
GAL-2	Liu et al., 2001

Table 1 Legend: IL, interleukin; TGF, transforming growth factor
 TNF, tumour necrosis factor; IFN, interferon; CTLA, cytotoxic T
 lymphocyte antigen; Fc(gamma)R, Fc(gamma)receptor; NRAMP, natural
 resistance associated macrophage protein; GAL, galactose permease;
 (x n), number of polymorphisms within gene.

Gene expression will be measured using microarrays, which contain hundreds of genes known to be important in the normal functioning of the cell and in the development of diseases like cancer and autoimmunity. These arrays allow us to take a snapshot of gene expression at a particular time in a particular cell type, snapshots that we can subsequently compare to see if particular genes are involved in the disease process. The data gathered will permit analysis of the relationship between different genes and the disease process. The development of novel therapies may be possible by our increased understanding of the genes crucial to the development ITP.

Medical Record Extraction Procedure:

During the defined ten-year study period, information on the following fields will be extracted from patient hospital records at registration, six-months following registration, and annually following registration using standard proforma. For study participants registered at The Royal London Hospital, these extractions will be undertaken by a three-person team comprising the study coordinator, the data manager, and a data specialist. Data pertaining to the aforementioned fields will be doubly entered into the electronic study database and cross-verified. Should inconsistencies arise during this check, the double extraction protocol will be repeated. At all other collaborating centres, local haematologists will be responsible for performing scheduled extractions and for forwarding the abstracted data to the chief investigator's team using a secured server.

Fields for Extraction:

Demographic Information: [Registration Form Only]

- Patient name
- Patient gender

- Patient date of birth
- Patient mailing address
- Consultant haematologist name
- Centre name
- Centre address
- Date of registration

Main ITP Information:

- Date of diagnosis [(Re-)Registration Forms Only]
- Platelets (count & date)
- Change of Diagnosis (yes/no) [1st Annual/Re-Registration Form Only]

Treatment: (yes/no; date, dosage & duration where applicable)

- Prednisolone
- IVIg
- Splenectomy (laparoscopic/standard technique)
- Anti-D
- Cyclic high-dose methylprednisolone
- Dexamethasone
- Danazol
- Azathioprine
- Cyclophosphamide
- Vinca alkaloids
- Mycophenolate
- Plasmapheresis/protein A immunoadsorption
- Interferon
- Cyclosporine
- Rituximab
- Platelet transfusion
- Red blood cell transfusion
- H. pylori treatment

Co-Morbid Conditions: (yes/no, date)

- Cataracts
- Long-bone fractures
- Type II diabetes
- Hypertension
- Peptic ulcers
- H. pylori infection
- Chronic renal failure or impairment
- Chronic liver disease
- Myocardial infarction
- Hepatitis C
- Splenomegaly
- Thyroid disease
- Depression/anxiety
- Miscarriage
- Cushing's syndrome
- Candida infections
- Pneumonia
- Mortality

Biochemical Fields (levels at diagnosis) [(Re-)Registration Only]

- Alanine transaminase
- Aspartate transaminase
- Alkaline phosphatase
- Bilirubin

Haematological Fields [(Re-)Registration Form Only]

- Haemoglobin (levels at diagnosis)
- White blood cells (levels at diagnosis)
- Blood group (A, B, AB & O; positive/negative)
- Marrow aspirate (yes/no, normal/abnormal at diagnosis)
- Trepine biopsy (yes/no, normal/abnormal at diagnosis)
- Direct agglutination test (positive/negative at diagnosis)

Immunological Fields [(Re-)Registration Form Only]

- Immunoglobulin (levels at diagnosis)
 - o IgA
 - o IgM
 - o IgG
- Anti-nuclear antibodies (levels at diagnosis)
- Autoantibody screen (positive/negative at diagnosis)

Coagulatory Fields (levels at diagnosis) [(Re-)Registration Form Only]

- Prothrombin time
- Activated partial prothrombin time
- Lupus anticoagulant
- Anticardiolipin antibody

Indium Scanning (48 hour spleen/liver ratio, date)

Bleeding Events: (yes/no, date, severity)

- cutaneous bleeds
- bleeds from the oral cavity
- epistaxis
- menorrhagia
- haematuria
- gastrointestinal bleeds
- intracranial haemorrhage
- muscle bleeds
- joint bleeds

Past Study Participants:

Death registries in England, Scotland, Wales, and Northern Ireland will be scanned to assess the status of past study participants. Living individuals from this cohort will be sent a mailing highlighting the substantive alterations to the study and providing a written means to opt out from further retrospective and prospective investigation. Blood samples will not be requested from these patients. However, the same fields of information will be extracted from their hospital records as from the records of prospectively enrolled study participants. These extractions will be performed by either the three-person team or local collaborating haematologists at the time of re-registration, defined as two weeks following the post-marked date of the study update mailing, and annually thereafter during the defined ten-year study period.

Medical Record Extraction Analysis:

Abstracted information from participant medical records will be used to conduct the qualitative and quantitative analyses highlighted in Appendix A1, which include estimations the burden of adult ITP in the United Kingdom, the natural progression of the disease, and the effectiveness of currently implemented therapies. These analyses will be conducted half-way through the study and at its conclusion in 2017; results from these investigations will be published in our monthly study newsletter and in The Platelet, the official newsletter of the ITP Support Organisation.

Communication of Study Progress:

Though study participants will not be actively involved in the investigation following registration, they will be kept closely apprised of study progress through a mailed and electronically posted monthly newsletter. They, too, will be provided with multiple means to contact the chief investigator's team regarding any questions or concerns throughout the duration of the study.

References:

- 1) T. L. McDowell, J. A. Symons, R. Ploski, O. Forre, G. W. Duff, *Arthritis Rheum* 38, 221-8 (1995)
- 2) S. John, et al., *Annals Of The Rheumatic Diseases* 57, 361-5 (1998)
- 3) A. Cantagrel, et al., *Arthritis Rheum* 42, 1093-100 (1999)
- 4) H. Hackstein, H. Kluter, L. Fricke, J. Hoyer, G. Bein, *Tissue Antigens* 54, 471-7(1999)
- 5) D. Fishman, et al., *J Clin Invest* 102, 1369-76 (1998)
- 6) O. Olomolaiye, N. A. Wood, J. L. Bidwell, *Eur J Immunogenet* 25, 267 (1998)

- 7) E. Bornscheuer, D. Zillikens, J. M. Schroder, M. Sticherling, *Dermatology* 198, 118–121 (1999)
- 8) D. M. Turner, et al., *Eur J Immunogenet* 24, 1–8 (1997)
- 9) P. A. Lympny, et al., *Tissue Antigens* 52, 573–8 (1998)
- 10) A. G. Wilson, J. A. Symons, T. L. McDowell, H. O. McDevitt, G. W. Duff, *Proc Natl Acad Sci USA* 94, 3195–9 (1997)
- 11) T. Siegmund, et al., *Thyroid* 8, 1013–7 (1998)
- 12) Y. Jiang, et al., *Immunogenetics* 51, 429–35 (2000)
- 13) D. P. Singal, J. Li, Y. Zhu, G. Zhang, *Tissue Antigens* 55, 44–7 (2000)
- 14) J. M. Heward, et al., *J Clin Endocrinol Metab* 84, 2398–401 (1999)
- 15) H. X. Liu, et al., *Proc Natl Acad Sci USA* 98, 9960–9964 (2001)

A10-2. In which parts of the research have patients, members of the public or service users been involved?

- As user-researchers
 As members of a research project group
 As advisor to a project
 As members of a departmental or other wider research strategy group
 None of the above

Please provide brief details if applicable:

A10-3. Could the research lead to the development of a new product/process or the generation of intellectual property?

- Yes No Not sure

Question(s) 11 disabled.

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 participant		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		
Venepuncture	> 1	1	Once at enrollment	One sample of blood (10 mL, ~2 teaspoonsful) will be taken from consenting study participants during a routinely scheduled venepuncture for platelet count analysis at outpatient clinics.

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	Average time taken	Details of additional intervention or procedure, who will undertake it, and what training they have

	participant	(mins/hours/days)	received.

A14. Will individual or group interviews/questionnaires discuss any topics or issues that might be sensitive, embarrassing 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?

The maximum duration of participation in the study for prospective and past participants will be ten and fifteen years respectively. Following enrollment and the collection of a 10 mL (~2 teaspoonsful) blood sample, no active participation will be required of study participants. This cohort will, however, be kept closely appraised of our progress and findings via a monthly study newsletter and an annual interactive presentation at The ITP Support Association convention.

Question(s) 16 disabled.

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

There is no additional potential for pain, discomfort, or lifestyle changes beyond that resulting from routine care. A 10 mL (~2 teaspoonsful) blood sample will be collected by a clinical nurse during a routinely scheduled venepuncture, with no further active participation required of study participants. The slight possibility of participant distress exists owing to investigator access to hospital records and data transmission and storage. These concerns have been mitigated, however, through detailed explanation of the precise window and content permitted for extraction and the utilisation of data encryption software, passwords, and a secure sever for data transmission and storage.

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

There will be no immediate benefit for study participants as a result of this research. However, our findings may ultimately provide insight into the progression and cumulative burden of adult ITP while possibly leading to changes in treatment guidelines among certain groups, e.g. identification of likely responders to splenectomy. In a recent survey of patient views, the inability to give a cause for the disorder and the side-effects of steroids were major points of worry (Watson et al., 2000). Information gathered from the registry may spawn novel etiological hypotheses for future testing and reveal the risk of such conditions as cataracts and osteoporosis among differently treatment study participants.

Reference:

1) S. Watson, P. H. Bolton-Maggs, Blood 96, 438a (2000)

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

There is no potential for adverse effects, pain, or discomfort among researchers. The time required to extract data from hospital records will be substantial and, in this manner, may be construed as a necessary and worthwhile cost among collaborating consultant hematologists.

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:

(i) Adults with ITP are typically referred to hospital centres where they will be seen by consultant haematologists. Potential prospective study participants will, therefore, comprise adult patients presenting at haematology clinics with low platelet counts ($< 150 \times 10^9$ platelets/L) and exhibiting no evidence of underlying thrombocytopenic (low-platelet) diseases following a standard ITP workup. Eligible past participants will be identified through a cross-check of death registries in England, Scotland, Wales, and Northern Ireland.

(ii) Notice of study activation will be made to consultant haematologists in both The Platelet and the British Journal of Haematology, official publications of The ITP Support Association and the British Society of Haematologists respectively. Prospective participants will be approached by collaborating consultant haematologists while eligible past participants will be sent a mailing highlighting key study amendments and means through which to opt out from further investigation.

(iii) Study recruitment will be overseen by the chief investigator's team as outlined in A6. Prospective and eligible past and participants will be presented with the opportunity to contact a member of the chief investigator's team via telephone to discuss any questions or concerns. Failure of eligible past participants to opt out from further investigation within two weeks of the post-marked date of the study update mailing will be construed an indication of continued informed consent.

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)

The principal inclusion criteria are patients eighteen years of age or older presenting with peripheral platelet counts below 150×10^9 /L and exhibiting no evidence of other underlying thrombocytopenic (low-platelet) diseases following a standard ITP workup.

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

Adult patients exhibiting evidence of other underlying thrombocytopenic diseases will be excluded from this study along with individuals hailing from vulnerable groups as defined by A24.

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.

- No participants from any of the above groups

Question(s) 24 1–5–25 disabled.

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.

Local consultant haematologists will alert the study coordinator to potential participants so that recruitment and informed consent can be directed by the chief investigator's team. These local collaborators will then download consent forms and information sheets from a secure study server and discuss their contents with eligible patients, who will have an additional opportunity to pose questions or concerns with members of the chief investigator's team directly by telephone. Written consent will be taken locally and stored in the patient's notes locally, with a copy forwarded to the study data manager at The Royal London Hospital.

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?

There will be no time limit for potential participants to decide whether or not take part in our research. Eligible adult ITP patients will be welcome to join at any point during the defined ten-year study period.

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.)

Where English is not the eligible patient's first language, recruitment will only take place following discussion through an interpreter. At The Royal London Hospital, the Advocates (interpreters) Department liaises closely with clinicians; advocates routinely attend our clinics to explain diagnoses and possible treatments, and we will seek their help in explaining the study details to patients whose first language is not English. We will ask that collaborators at other centres employ interpreters as required.

Question(s) 30 disabled.

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

A32a. Will the research participants' General Practitioner (and/or any other health professional responsible for their care) 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/health professional with a version number and date.

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

Question(s) 32b disabled.

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. Insurance/indemnity to meet potential legal liabilities

Note: References in this question to NHS indemnity schemes include equivalent schemes provided by Health and Personal Social Services (HPSS) in Northern Ireland.

A35-1. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) for harm to participants arising from the management of the research?

Note: Where a NHS organisation has agreed to act as the sponsor, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For all other sponsors, describe the arrangements and provide evidence.

- NHS indemnity scheme will apply
 Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A35-2. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of the sponsor(s) or employer(s) for harm to participants arising from the design of the research?

Note: Where researchers with substantive NHS employment contracts have designed the research, indemnity is provided through NHS schemes. Indicate if this applies (there is no need to provide documentary evidence). For other protocol authors (e.g. company employees, university members), describe the arrangements and provide evidence.

- NHS indemnity scheme will apply to all protocol authors

- Other insurance or indemnity arrangements will apply (give details below)

Please enclose a copy of relevant documents.

A35-3. What arrangements will be made for insurance and/or indemnity to meet the potential legal liability of investigators/collaborators and, where applicable, Site Management Organisations, arising from harm to participants in the conduct of the research?

Note: Where the participants are NHS patients, indemnity is provided through NHS schemes or through professional indemnity. Indicate if this applies to the whole of the study (there is no need to provide documentary evidence). Where non-NHS sites are to be included in the research, including private practices, describe the arrangements which will be made at these sites and provide evidence.

- All participants will be recruited at NHS sites and NHS indemnity scheme or professional indemnity will apply
 Research includes non-NHS sites (give details of insurance/indemnity arrangements for these sites below)

Please enclose a copy of relevant documents.

Question(s) 36 disabled.

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

If other/none of the above, give details and justify:

The results of the study will be incorporated into the study coordinator's PhD dissertation in Public Health and Primary Care at the University of Cambridge. An original copy of this manuscript will be held in the Special Collections branch of the University Library.

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

Results from our investigation will be published in The Platelet, the official newsletter of The ITP Support Association, as well as our bimonthly study newsletter. Though directed toward research participants, their families, and haematologists, this latter publication will be freely available to all members of the public via our online study site, www.ukitregistry.com. We will additionally seek to present these findings at patient-group gatherings throughout the United Kingdom.

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:

The chief investigator's team will consist of the study coordinator, the data manager, and extraction specialist. These three full-time positions will be held by individuals experienced in epidemiology, health administration, and medical research respectively. As non-clinical, honorary NHS employees, these individuals would not normally have access to examine patient medical records within the NHS. The Joint Research Office for Barts and the London NHS Trust and Barts and the London, Queen Mary's School of Medicine and Dentistry, however, has agreed to authorise them access as agents of this study. The chief investigator will ultimately oversee these posts and ensure study adherence with appropriate NHS guidelines.

The names and addresses of participants will be collected by the study coordinator to provide an accurate means of follow-up and direct communication in the event of major substantive developments, including investigatory amendments and study termination. The initial information pro-forma completed by collaborating consultant haematologists upon patient registration (or re-registration) will contain fields for both participant name and address. Upon online receipt of this pro-forma via a Secure Sockets Layer (SSL) 128-bit encrypted, password-protected server, the study coordinator will allocate each participant a unique reference number. This number will be shared with the collaborating consultant haematologist and will be used for all subsequent data collection, storage, and transfer, including the semi-anonymisation of participant blood samples prior to delivery to the Molecular Haematology Laboratory in the Institute for Cell and Molecular Studies. The key to these reference numbers will be encrypted and stored separately from the study database on the chief investigator's personal, password-protected NHS computer, which will be restricted to the study coordinator and the chief investigator.

The primary study database (MS Access) will be stored on a password-protected Barts and the London, Queen Mary's School of Medicine and Dentistry computer in the UK ITP study office on the 4th floor of the Pathology and Pharmacy Building at The Royal London Hospital, a location restricted to Trust haematology staff. The study database will be encrypted using the Windows XP Encrypting File System (EFS). Separate back-ups of the study database and the reference number key will be performed weekly using two storage drives stored in secure, fire-proof locations within the building.

Fully anonymised-data will be shared annually with the study sponsor, GlaxoSmithKline, and the Paediatric and Adult Intercontinental Registry on Chronic ITP (PARC-ITP) Study based in Basel via electronic transfer on a password-protected, SSL 128-bit encrypted server. These groups will be permitted to conduct ethically approved analyses on this data, but will be required to destroy all received information by the date indicated in A44.

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:

As detailed in A39, collaborating consultant haematologists will supply participant names and addresses on the initial information pro-forma in order to provide the study coordinator with a means of accurate follow-up and direct communication to relay major developments. As with all information pro-forma used in the study, the initial information pro-forma will be downloaded and submitted via an SSL 128-bit encrypted, password-protected server. Upon receipt of this document, the study coordinator will allocate each participant with a unique reference number. This number will be shared with the collaborating consultant haematologist alone and will be used for all subsequent data collection, storage, and transfer, including the semi-anonymisation of participant blood samples prior to delivery to the Molecular Haematology Laboratory at the Institute for Cell and Molecular Studies. The reference number key will be encrypted and stored separately from the primary study database on the chief investigator's password-protected personal NHS computer, which will be restricted solely to the study coordinator and the chief investigator.

The primary study database (MS Access) will be stored on a password-protected Barts and the London, Queen Mary's School of Medicine and Dentistry computer in the UK ITP study office on the 4th floor of the Pathology and Pharmacy Building at The Royal London Hospital, a location restricted to trust haematology staff. The study database will be encrypted using the Windows XP Encrypting File System (EFS). Separate back-ups of the primary database and the reference number key will be performed weekly using two storage drives stored in secure, fire-proof locations within the building.

Fully anonymised data will be shared annually with the study sponsor, GlaxoSmithKline (GSK), and the PARC-ITP Study based in Basel via electronic transfer on a password-protected, SSL 128-bit encrypted server. These groups will be permitted to conduct ethically approved analyses on this data, but will be required to destroy all received information by the time indicated in A44.

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

Analysis of collected data will be open to the named UK Adult ITP study investigators and will take place at The Royal London Hospital. A fully anonymised subset of this data will be shared annually with GSK and the PARC-ITP Study and will thus be open to analysis by GSK epidemiologists worldwide and named PARC study investigators in Basel, Switzerland. These researchers will be required to adhere to their respective organisation's procedures for data protection and analysis.

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

The study coordinator will act as custodian of the data generated by the study and will be overseen by the chief investigator, who will hold ultimate decision-making power on study-related matters.

A43. Who will have access to research participants' or potential research participants' health records or other personal information? Where access is by individuals outside the normal clinical team, justify and say whether consent will be sought.

Access to research participants' health records and other personal information will be confined to the normal clinical team at external study centres. Such access, however, will be granted to members of the chief investigator's team. The study coordinator, data manager, and extraction specialist have been authorised by the Joint Research Office for Barts and the London NHS Trust and Barts and the London, Queen Mary's School of Medicine and Dentistry to extract data from participant hospital records at The Royal London Hospital as agents of this study.

Informed consent will be sought and required for patient participation in the study.

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

20 Years 00 Months

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

The entirety of information collected from this study will be stored on an encrypted MS Access database on a password-protected Barts and the London, Queen Mary's School of Medicine and Dentistry computer in the UK ITP study office on the 4th floor of the Pathology and Pharmacy Building at The Royal London Hospital. Access to this database will be restricted to the study coordinator, the data manager, and the chief investigator. The reference number key used to semi-anonymise collected data will be encrypted and stored separately from the primary study database on the chief investigator's password-protected personal NHS computer, which will be restricted to the study coordinator and the chief investigator. Separate back-ups of these files will be performed weekly using two storage drives stored in secure, fire-proof locations within the building.

DNA and RNA will be extracted from participant blood samples at the Molecular Haematology Laboratory in the Institute for Cell and Molecular Studies and stored in the trust tissue bank.

The study coordinator will act as primary custodian of this data under the supervision of the chief investigator.

A fully-anonymised subset of data will be shared annually with GlaxoSmithKline and the PARC-ITP Study. This data will be stored on encrypted servers and will be managed by delegated analysts and investigators. The entirety of information collected from this study will be stored on an encrypted MS Access database on a password-protected Barts and the London, Queen Mary's School of Medicine and Dentistry computer in the UK ITP study office on the 4th floor of the Pathology and Pharmacy Building at The Royal London Hospital. Access to this database will be restricted to the study coordinator, the data manager, and the chief investigator. The reference number key used to semi-anonymise collected data will be encrypted and stored separately from the primary study database on the chief investigator's password-protected personal NHS computer, which will be restricted to the study coordinator and the chief investigator. Separate back-ups of these files will be performed weekly using two storage drives stored in secure, fire-proof locations within the building.

DNA and RNA will be extracted from participant blood samples at the Molecular Haematology Laboratory in the Institute for Cell and Molecular Studies and stored in the trust tissue bank.

The study coordinator will act as primary custodian of this data under supervision from the chief investigator.

A fully-anonymised subset of data will be shared annually with GlaxoSmithKline and the PARC-ITP Study. This data will be stored on encrypted servers and will be managed by delegated analysts and investigators.

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
- Review within the Chief Investigator's institution or host organisation
- Review within the research team
- Review by educational supervisor
- Other

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:

The proposed study has been formally assessed by peers within the Institute of Cell and Molecular Sciences, GlaxoSmithKline Worldwide Epidemiology's Protocol Review Forum, and the Joint Research Office for Barts and the London NHS Trust and Barts and the London, Queen Mary's School of Medicine and Dentistry.

Each review entailed a formal critique of the study protocol, recommendations for further improvement (if any), resubmission of the amended protocol (if requested), and a final verdict with regards to clearance. Assessors rigorously evaluated the justification, feasibility, and ethics of the proposed research. All three assessments were favourable and are included within this ethics application.

Finally, the PARC-ITP Study, which will annually receive a fully-anonymised subset of our data, was assessed in detail and approved by the Ethics Committee of Basel (EKBB) in October 2003.

A45-2. How have the statistical aspects of the research been reviewed? (Tick as appropriate)

- Review by independent statistician commissioned by funder or sponsor
 Other review by independent statistician
 Review by company statistician
 Review by a statistician within the Chief Investigator's institution
 Review by a statistician within the research team or multi-centre group
 Review by educational supervisor
 Other review by individual with relevant statistical expertise

In all cases give details below of the individual responsible for reviewing the statistical aspects. If advice has been provided in confidence, give details of the department and institution concerned.

	Title:	Forename/Initials:	Surname:
	Dr.	Michael	Colopy
Department:	Worldwide Epidemiology		
Institution:	GlaxoSmithKline Inc.		
Work Address:	Five Moore Drive, P.O. Box 13398 Research Triangle Park, North Carolina United States of America		
Postcode:	22709		
Telephone:	001-919-483-5414		
Fax:	001-919-315-8747		
Mobile:			
E-mail:	mike.w.colopy@gsk.com		

Please enclose a copy of any available comments or reports from a statistician.

Question(s) 46-47 disabled.

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

Statistically assessed outcomes measures utilised in this observational study fall into one of three analytic fields shown below.

Co-morbid Condition Outcomes: (prior to and post both diagnosis and treatment)

- a) cataracts
- b) long-bone fractures
- c) type II diabetes
- d) hypertension
- e) peptic ulcers
- f) H. pylori infection
- g) chronic renal failure
- h) chronic liver disease
- i) myocardial infarction
- j) hepatitis C
- k) splenomegaly
- l) thyroid disease
- m) depression/anxiety
- n) Cushing's syndrome
- o) pneumonia

- p) Candida infection
- q) mortality

Disease Progression & Treatment Effectiveness Outcomes:

- a) change platelet count since diagnosis, continuous
- b) highest platelet count, dichotomous [$< 50,000 \times 10^9/L$ & $\geq 50,000 \times 10^9/L$]
- c) bleeding event, ranked categorical (0, 1, 2)

Genetic Outcomes:

- a) single nucleotide polymorphism sequences within the following genes
IL-1 (alpha), IL-2, IL-4, IL-4R, IL-6, IL-8, IL-10 [3X], TGF-(beta)[2X],
TNF-(alpha), IFN-(gamma), Fc(gamma)RII & III, NRAMB-1, CTLA-4, GAL-2

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

Outcome measures that will be used for primarily descriptive and qualitative purposes will include the following.

- a) participant age & gender
- b) platelet counts over time
- c) number and proportion of participants treated v. untreated
 - i. among cohort less than 60 years old, non-hypertensive, and without a history of peptic ulcers presenting with a platelet count $20 \times 10^9/L$; $X < 30 \times 10^9/L$, and no bleeding history
 - ii. among cohort presenting with a platelet count $30 \times 10^9/L$; $X < 50 \times 10^9/L$ and no bleeding history
 - iii. with splenectomy among cohort failing either prednisolone or IVIg treatment alone
 - iv. with splenectomy among cohort failing initial prednisolone treatment alone
 - v. with splenectomy among cohort failing initial IVIg treatment alone
- d) genome-wide gene expression patterns
 - i. between participants with severe and non-severe ITP at diagnosis
 - ii. between participants responsive and non-responsive to prednisolone treatment (among the primarily-referred, prednisolone-treated population only)

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.

Over a four-year period, approximately 600 adult ITP patients were successfully recruited in the previous version of this study. This total, importantly, represents a combination of both prevalent and incident cases. Our prospective recruitment, however, will largely capture incident cases alone. We, therefore, estimate a slightly lower prospective recruitment rate than would be indicated by our prior findings and believe that we will be able recruit an additional 1000 participants, resulting in a total cohort size of 1600.

A51. How was the number of participants decided upon?

View A50. Adult ITP is a relatively rare condition. We will, therefore, seek to enroll as many study participants as possible to ensure the external validity of our findings.

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

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.

The qualitative and statistical methods of analysis that will be utilised in this study are illustrated in Appendix A1.

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:

Though data will be collected, stored, and analysed in the United Kingdom by the chief investigator and study coordinator, a fully-anonymised subset of data will be forwarded annually to the study sponsor, GSK, and the PARC-ITP Study based in Basel, Switzerland.

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 |
|--|----------------------------|
| <input checked="" type="checkbox"/> Acute teaching NHS Trusts | ~20 |
| <input checked="" type="checkbox"/> Acute NHS Trusts | ~20 |
| <input type="checkbox"/> NHS Primary Care Trusts or Local Health Boards in Wales | |
| <input type="checkbox"/> NHS Trusts providing mental healthcare | |
| <input checked="" type="checkbox"/> NHS Health Boards in Scotland | ~10 |
| <input checked="" type="checkbox"/> HPSS Trusts in Northern Ireland | ~5 |
| <input type="checkbox"/> GP Practices | |
| <input type="checkbox"/> NHS Care Trusts | |
| <input type="checkbox"/> Social care organisations | |
| <input type="checkbox"/> Prisons | |
| <input type="checkbox"/> Independent hospitals | |
| <input type="checkbox"/> Educational establishments | |
| <input type="checkbox"/> Independent research units | |

Other (give details)

Other:

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

The chief investigator has formed a five-member UK Adult ITP Registry Monitoring Committee (UKAIRMC), which will be charged with tracking recruitment rates, monitoring collected data, and auditing medical record extraction, blood sample procurement, and data protection methods. This committee will convene yearly and report its findings to the Joint Research Office for Barts and the London NHS Trust and Barts and the London, Queen Mary's School of Medicine and Dentistry.

Question(s) 57a disabled.

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: GlaxoSmithKline Research Development Ltd.
 Address: 980 Great West Road
 Brentford
 Middlesex
 Post Code: TW8 9GS
 UK contact: Dr. Jamie Robinson
 Telephone: 020-8966-2910
 Fax: 020-8966-2475
 Mobile:
 E-mail: noah.j.robinson@gsk.com
 Amount (£): 267,875 Duration: 24 Months

Organisation: The ITP Support Association
 Address: Synehurste, Kimbolton Road
 Bolnhurst
 Bedford
 Post Code: MK44 2EW
 UK contact: Mrs. Shirley Watson
 Telephone: 012-3437-6559
 Fax: 012-3437-6559
 Mobile:
 E-mail: shirley@itpsupport.org.uk
 Amount (£): 40,000 Duration: 12 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**Lead sponsor** (*must be completed in all cases*)

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

Barts and the London NHS Trust

Status:

 NHS or HPSS care organisation Academic Pharmaceutical industry Medical device industry Other*If Other, please specify:*

Address: Joint Research Office, 24–26 Walden Street

Whitechapel

London

Post Code: E1 2AN

Telephone: 020–7882–7260

Fax: 020–7882–7276

Mobile:

E–mail: gerry.leonard@bartsandthelondon.nhs.uk

Sponsor's UK contact point for correspondence with the main REC (*must be completed in all cases*)

Title: Mr

Forename/Initials: Gerry

Surname: Leonard

Work Address: Joint Research Office, 24–26 Walden Street

Whitechapel

London

Post Code: E1 2AN

Telephone: 020–7882–7260

Fax: 020–7882–7276

Mobile:

E–mail: gerry.leonard@bartsandthelondon.nhs.uk

Co-sponsors**Are there any co-sponsors for this research?** Yes No**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 taking part in 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 investigator/collaborator have any direct personal involvement (e.g. financial, share-holding, personal relationship etc.) in the organisations sponsoring or funding the research that may give rise to a possible conflict of interest?

Yes No

If yes, give details including the amount of any monetary payment or the basis on which this will be calculated:

In 2005, the chief investigator served as the Medicines Development Centre (MDC)–Oncology Director at GSK. He still holds the initial volume of company shares (< £ 5,000) he was provided upon starting this position. The chief investigator additionally serves as a member of the ITP Support Association Advisory Board.

In 2006, the study coordinator was employed by GSK Worldwide Epidemiology as a summer student and subsequently as an independent contractor.

These past and present ties are not believed to pose a potential conflict of interest.

A65. Research reference numbers: (give any relevant references for your study):

Applicant's/organisation's own reference number, e.g. R&D (if available): ICMS/PR/07/023

Sponsor's/protocol number:

Funder's reference number:

WEUSRTP1121 (GSK)

Project website: www.ukitregistry.com

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

Title: Professor

Forename/Initials: Adrian

Surname: Newland

Post:

Professor of Haematology

Qualifications:

MA MBChB FRCP PRCPPath

Organisation:

Barts and the London, Queen Mary's School of Medicine and Dentistry

Work Address:

Rm 411, Pathology & Pharmacy Building

The Royal London Hospital

80 Newark Street, London

Postcode:

E1 2ES

Telephone:

020-3246-1102

Fax:

020-3246-0351

Mobile:

E-mail: a.c.newland@qmul.ac.uk

Title: Mr. Forename/Initials: Ameet Surname: Sarpatwari

Post: Study Coordinator; PhD Student in Public Health and Primary Care

Qualifications: BA(Hons) M.Phil

Organisation: University of Cambridge

Work Address: Rm 405, Pathology & Pharmacy Building

The Royal London Hospital

80 Newark Street, London

Postcode: E1 2ES

Telephone: 020-3246-0230

Fax: 020-3246-0351

Mobile:

E-mail: avs31@medschl.cam.ac.uk

Title: Dr. Forename/Initials: Yu-mei Surname: Chang

Post: Sudy Data Manager

Qualifications: BSc MSc PhD

Organisation: Barts and the London, Queen Mary School of Medicine and Dentistry

Work Address: Rm 405, Pathology & Pharmacy Building

The Royal London Hospital

80 Newark Street, London

Postcode: E1 2ES

Telephone: 020-3246-0230

Fax: 020-3246-0351

Mobile:

E-mail: y.m.chang@qmul.ac.uk

Question(s) 67 disabled.

PART A: Summary of Ethical Issues

A68. What are the main ethical issues with the research?

Summarise the main issues from the participant's point of view, and say how you propose to address them.

Primary ethical concerns surrounding the proposed research include adequate data protection and ethical incorporation of past study participants. As part of this study, the chief investigator's team and collaborating consultant haematologists will have access to potentially sensitive medical records. The information and window permissible for extraction have, therefore, been explicitly codified in both the protocol and the participant study overview.

The transfer of this abstracted data will additionally take place over a SSL 128-bit encrypted, password-protected server. While participant names and addresses will be collected via initial information pro-forma to enable accurate follow-up and a direct means of emergency contact, all subsequent data collection, storage, and transfer will utilise uniquely allocated participant reference numbers. Further protective measures, described in detail in A39, will be implemented alongside these procedures to ensure the protection of patient identity and data.

While the proposed study remains fundamentally similar to the investigation initiated in 2002, living past participants will be provided with a first-class mailing detailing changes to the study protocol, the chief

investigator's team, and the primary financial sponsors. This study update will additionally specify means through which past participants may withdraw from further investigation and contact member of the chief investigator's team to address outstanding questions or concerns. A window of two-weeks following the post-marked date of these mailings will allotted for study withdrawal prior to investigatory commencement. Like all prospectively enrolled study participants, remaining past participants will be permitted to withdraw at any point during the investigation.

Indicate any issues on which you would welcome advice from the ethics committee.

We welcome advice from the Ethics Committee as to whether we should include a postage-paid, return-envelope in our mailing to past participants as a possible means through which to withdraw from further investigation. At present, we plan on simply providing the phone number and mailing address of our central study office.

Question(s) 69 disabled.

PART A: Student Page**A70. Give details of the educational course or degree for which this research is being undertaken:**

Name of student:

Ameet Vilas Sarpatwari

Name and level of course/degree:

Public Health and Primary Care, PhD

Name of educational establishment:

University of Cambridge

Name and contact details of educational supervisor:

Dr. Simon Sanderson
 Co-Supervisor
 Lecturer in Public Health and Primary Care
 Department of Public Health and Primary Care
 University of Cambridge
 Phone: 012-2374-1164
 Email: simon.sanderson@srl.cam.ac.uk

Dr. Drew Provan
 Co-Supervisor
 Senior Lecturer in Clinical Haematology
 Centre for Haematology
 St. Bartholomew's & The Royal London School of Medicine & Dentistry
 London E1 2ES
 Phone: 020-3246-0335
 Email: a.b.provan@qmul.ac.uk

A71. Declaration of educational supervisor

I have read and approved both the research proposal and this application for the ethical review. I am satisfied that the scientific content of the research is satisfactory for an educational qualification at this level. I undertake to fulfil the responsibilities of a supervisor as set out in the Research Governance Framework for Health and Social Care.

Signature:

Print Name: Drs. Drew Provan & Simon Sanderson

Date: 28/05/2007 (dd/mm/yyyy)

A one-page summary of the supervisor's CV should be submitted with the application

PART B: Section 1 – Conduct of the research at local sites

From the answer given to question A6, it is assumed that:

- *Local Principal Investigators will not be appointed at each research site participating in this study.*
- *Applications for site-specific assessment by local Research Ethics Committees will not be required.*
- *There will be no requirement for individual research sites to be approved by the main REC as part of the ethical review.*

The following general information should be provided to the main REC about the local conduct of the study.

1. What research procedures will be carried out at individual research sites?

Two key research procedures will be carried out at individual research sites. First, participant blood samples (10 mL, ~2 teaspoonsful) will be drawn by clinical nurses during routinely scheduled venepuncture. Second, the chief investigator's team and consultant haematologists will be charged with extracting information from participant medical records at The Royal London Hospital and collaborating study centres respectively using standard information pro-forma.

2. Are any ethical issues likely to arise at individual sites that are not covered in the protocol for the study and if so how will these be addressed?

For example, a need for particular facilities, or to notify local clinicians or departments about the research, or to arrange additional local support for participants.

No.

3. How will the Chief Investigator and his/her team supervise the conduct of the research at individual sites? What responsibilities will be delegated to local collaborators?

The chief investigator has formed a five-member UK Adult ITP Registry Monitoring Committee (UKAIRMC), which will be charged with tracking recruitment rates, monitoring collected data, and auditing medical record extraction, blood sample procurement, data protection methods. This committee will convene yearly and report its findings to the Joint Research Office for Barts and the London NHS Trust and Barts and the London, Queen Mary's School of Medicine and Dentistry.

Study participants will be informed of means through which to direct concerns, questions, or complaints to the chief investigator's team. Any complaints or recommendations that are received will be forwarded to the UKAIRMC.

A formal validation analysis will be conducted mid-way through the study at randomly selected sites to assess the accuracy of data extraction and entry procedures. Results from this investigation will be similarly forward to the UKAIRMC.

Management approval to proceed with the research will be required from the R&D office for each NHS care organisation in which research procedures are undertaken. The Site-Specific Information Form should be used to apply for R&D approval at NHS sites in England, Wales and Scotland.

PART B: Section 4 – Use of existing stored human tissue (or other human biological materials)

1. What types of human tissue or other biological material will be included in the study?

In the previous version of this study, forty–five percent of past participants contributed blood samples (10 mL, ~2 teaspoonsful) during routinely taken venepuncture at outpatient haematology clinics. Participant DNA was extracted from these samples and will be used in our investigation of associations of single nucleotide polymorphisms (SNPs) with disease severity and treatment effectiveness.

2. Will the samples be released to the researcher:

In fully anonymised form? (*link to stored tissue and data is broken*)

Yes No

In linked anonymised form? (*linked to stored tissue but donor not identifiable to researchers*)

Yes No

In a form in which the donor could be identifiable to researchers?

Yes No

If Yes, please justify:

3. What types of test or analysis will be carried out on the samples?

A full description of the analyses to be carried out on participant DNA samples is provided in Appendix A1. Briefly, we will conduct tests of the association of both disease severity and treatment effectiveness with single nucleotide polymorphisms (SNPs) located within the following genes.

Table of Genes for SNP Testing

- A. IL–1(alpha)
- B. IL–2
- C. IL–4
- D. IL–4R
- E. IL–6
- F. IL–8
- G. IL–10 [3X]
- H. TGF–(beta) [2X]
- I. TNF–(alpha)
- J. IFN–(gamma)
- K. Fc(gamma)RII & III
- L. NRAMP–1
- M. CTLA–4
- N. GAL–2

Note: [NX] indicates the number of SNPs to be investigated within a specified gene.

4. Has consent been obtained previously from donors to use stored samples for this purpose?

Yes No

If No, is it proposed to seek further consent? If not, please justify.

Consent has been previously obtained from past study participants to test for single nucleotide polymorphisms within all of the aforementioned genes except GAL–2 & IL–8. Living past participants will be sent a mailing

highlighting substantive study alterations, including the proposed addition of GAL-2 & IL-8 for SNP testing, and written means through which to opt out from further investigation. Deceased past participants will not be included in the study.

5. Will the research involve the analysis of human DNA in the samples?

Yes No

6. Is it possible that the research could produce findings of clinical significance for individuals? (May include relatives as well as donors)

Yes No

7. If so, will arrangements be made to notify the individuals concerned?

Yes No Not applicable

If No, please justify. If Yes, say what arrangements will be made and give details of the support or counselling service.

8. Who is the holder of the samples?

Name of the research tissue bank (or other collection):

The Royal London Hospital Tissue Bank

Does the bank/collection hold a licence from the Human Tissue Authority for storage and use of human tissue in research?

Yes No

REC reference no. (if the bank/collection is ethically approved):

12197 HTRC

Details of the organisation with responsibility for the bank:

Organisation: Research Office for Barts & the London NHS Trust & Queen Mary's SMD

Contact point (e.g. tissue bank manager):

Title: Forename/Initials: Surname:

Ms. Belinda Seeto

Role: Human Tissue Resource Centre Project Manager

Work Address: G15 Ground Floor, Pathology Department
St. Bartholomew's Hospital
West Smithfield, London

Postcode: EC1A7BE

Telephone: (0)20-7601-7521

Fax: (0)20-7601-8593

Mobile:

E-mail: belinda.seeto@bartsandthelondon.nhs.uk

9. What will happen to the samples at the end of the research?

- Destruction
- Return to current holder of the samples
- Transfer to another tissue bank
(If the bank is in England, Wales or Northern Ireland a licence from the Human Tissue Authority will be required to store the tissue for possible further research.)
- Storage by research team pending ethical approval for use in another project
(Unless the researcher holds a licence from the Human Tissue Authority, a further application for ethical review should be submitted before the end of this project.)
- Storage by research team as part of a new research tissue bank
(The bank will require a licence from the Human Tissue Authority. A separate application for ethical review of the tissue bank may also be submitted.)
- Not yet known

Please give further details of the proposed arrangements:

PART B: Section 5 – Use of newly obtained human biological materials**1. What types of human tissue or other biological material will be included in the study?**

Upon registration, one blood sample (10 mL, ~2 teaspoonsful) will be collected from each study participant during a normally scheduled venepuncture. Participant DNA and RNA (where possible) will be extracted from these samples and will be used in our investigation of associations of single nucleotide polymorphisms (SNPs) with disease severity and treatment effectiveness.

2. Who will collect the samples?

Each sample will be drawn by a clinical nurse serving as a routine member of the patient's care team.

3. Will the samples be: (Tick as appropriate)

- Obtained primarily for research purposes?
 Surplus (i.e. left over from tissue taken in the course of normal clinical care for diagnostic or therapeutic purposes)?

4. Will informed consent be obtained from donors for use of the samples:

In this research?

Yes No

In future research?

Yes No

5. Will the samples be stored:

In fully anonymised form? (*link to donor broken*)

Yes No

In linked anonymised form? (*linked to donor but donor not identifiable to researchers*)

Yes No

If Yes, say who will have access to the code and personal information about the donor.

The key to the assigned reference numbers will be encrypted and stored separately from the study database on the chief investigator's personal, password-protected NHS computer, and will be restricted to the study coordinator and the chief investigator alone.

In a form in which the donor could be identifiable to researchers?

Yes No

If Yes, please justify:

6. What types of test or analysis will be carried out on the samples?

A full description of analyses to be carried out on participant DNA and RNA samples is provided in Appendix A1. Briefly, we will conduct tests of the association of both disease severity and treatment effectiveness with

single nucleotide polymorphisms (SNPs) located within the following genes.

Table of Genes for SNP Testing

- A. IL-1(alpha)
- B. IL-2
- C. IL-4
- D. IL-4R
- E. IL-6
- F. IL-8
- G. IL-10 [3X]
- H. TGF-(beta) [2X]
- I. TNF-(alpha)
- J. IFN-(gamma)
- K. Fc(gamma)RII & III
- L. NRAMP-1
- M. CTLA-4
- N. GAL-2

Note: [NX] indicates the number of SNPs to be investigated within a specified gene.

With regards to RNA, a descriptive comparison of gene expression patterns will be conducted between participants exhibiting severe and non-severe ITP at diagnosis and participants responsive to and non-responsive to prednisolone treatment.

7. Will the research involve the analysis of human DNA in the samples?

- Yes No

8. Is it possible that the research could produce findings of clinical significance for individuals? (May include relatives as well as donors)

- Yes No

9. If so, will arrangements be made to notify the individuals concerned?

- Yes No Not applicable

If No, please justify. If Yes, say what arrangements will be made and give details of the support or counselling service.

10. Give details of where the samples will be stored, who will have access and the custodial arrangements.

Participant genetic samples will be held by The Royal London Hospital Tissue Bank, a research tissue bank registered with the Human Tissue Resource Centre (12197 HTRC) at Barts and the London NHS Trust. The chief investigator will serve as sole custodian of these samples.

11. What will happen to the samples at the end of the research?

- Destruction
- Transfer to research tissue bank
(If the bank is in England, Wales or Northern Ireland a licence from the Human Tissue Authority will be required to store the tissue for possible further research.)
- Storage by research team pending ethical approval for use in another project
(Unless the researcher holds a licence from the Human Tissue Authority, a further application for ethical review should be submitted before the end of this project.)
- Storage by research team as part of a new research tissue bank
(The bank will require a licence from the Human Tissue Authority. A separate application for ethical review of the tissue bank may also be submitted.)
- Not yet known

Please give further details of the proposed arrangements:

The Royal London Hospital Tissue Bank will hold our genetic samples following completion of our research. It is registered with the Human Resource Tissue Centre (12197 HTRC), a subgroup of The Joint Research Office for Barts and the London NHS Trust and Barts and the London, Queen Mary's School of Medicine and Dentistry.

PART B: Section 7 – Declarations**Declaration by Chief Investigator**

1. The information in this form is accurate to the best of my knowledge and belief and I take full responsibility for it.
2. I undertake to abide by the ethical principles underlying the Declaration of Helsinki and good practice guidelines on the proper conduct of research.
3. 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.
4. 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.
5. I undertake to submit annual progress reports setting out the progress of the research.
6. 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.
7. I understand that research records/data may be subject to inspection for audit purposes if required in future.
8. 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.
9. 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 held by the main REC until at least 3 years after the end of the study.
 - May be disclosed to the operational managers or the appointing body for the REC in order to check that the application has been processed correctly or to investigate any complaint.
 - May be seen by auditors appointed by the National Research Ethics Service to undertake accreditation of the REC.
 - Will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.

Optional – please tick as appropriate:

- I would be content for members of other RECs to have access to the information in the application in confidence for training purposes. All personal identifiers and references to sponsors, funders and research units would be removed.

Signature:

Print Name: Dr. Drew Provan

Date: 03/07/2007 (dd/mm/yyyy)

Declaration by the sponsor's representative

If there is more than one sponsor, this declaration should be signed on behalf of the co-sponsors by a representative of the sponsor nominated to take the lead for the REC application.

I confirm that: *(tick as appropriate)*

- This research proposal has been discussed with the Chief Investigator and agreement in principle to sponsor the research is in place.
- An appropriate process of scientific critique has demonstrated that this research proposal is worthwhile and of high scientific quality.*
- Any necessary indemnity or insurance arrangements, as described in question A35, will be in place before this research starts.
- Arrangements will be in place before the study starts for the research team to access resources and support to deliver the research as proposed.
- Arrangements to allocate responsibilities for the management, monitoring and reporting of the research will be in place before the research starts.
- The duties of sponsors set out in the NHS Research Governance Framework for Health and Social Care will be undertaken in relation to this research.**

* Not applicable to student research (except doctoral research).

** Not applicable to research outside the scope of the Research Governance Framework.

Signature:

Print Name: Dr. David Jackson

Post: Research Ethics Facilitator

Organisation: Barts and the London NHS Trust

Date: 28/05/2007 (dd/mm/yyyy)

Site-Specific Information Form

Does this application relate to a research site for which the NHS (or HPSS in Northern Ireland) is responsible or to a non-NHS research site?

- NHS site
 Non-NHS site

For HPSS sites in Northern Ireland, separate arrangements are in place for R&D applications. There is no need to complete questions marked "R&D only" on this form.

This question must be completed before proceeding. The filter will customise the form, disabling questions which are not relevant to this application.

The data in this box is populated from Part A:

Short title and version number:
 United Kingdom Adult ITP Registry

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

Project reference number from above REC: 07/H0718/57

Name of NHS care organisation to which application is being made for permission to conduct the research:
 Barts and the London NHS Trust

NHS organisation reference (for R&D office use only):

1. Title of the research *(populated from A1)*

Full title: United Kingdom Adult Idiopathic Thrombocytopenic Purpura (ITP) Registry: An Investigation of Disease Progression, Treatment Effectiveness, and Co-morbid Conditions
 Key words: Thrombocytopenia
 ITP
 Adult
 PARC

2. Name of Chief Investigator *(populated from A2)*

Title: Forename/Initials: Surname:
 Dr. Drew Provan

3. Name of organisation acting as lead sponsor for the study *(populated from A59)*

Barts and the London NHS Trust

4. Research reference numbers if known (populated from A65)

Applicant's/organisation's own reference number, e.g. R&D: ICMS/PR/07/023

Sponsor's/protocol number:

Funder's reference number: WEUSRTP1121 (GSK)

Project website: www.ukitregistry.com

6. Give the name of the NHS site within or through which the research will take place under the responsibility of the PI or Local Collaborator. Please give the name only. Further details of locations should be given in question 8. The name of the site is normally the name of the relevant NHS organisation. Each NHS general or dental practice is a separate site unless a formal consortium/network is in place.

Barts and the London NHS Trust

Is this a primary care site?

Yes No

If Yes, give the name of the primary care organisation responsible for the site below:

8. Specify all locations, departments, groups or units at which or through which research procedures will be conducted at this site and describe the activity that will take place.

List all locations/departments etc where research procedures will be conducted within the NHS organisation, describing the involvement in a few words. Where access to specific facilities will be required these should also be listed for each location.

Name the main location/department first. Include details of any centres at other NHS organisations where potential participants may be seen or 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.

	Location	Activity/facilities
1	Knutsford Ward	1. Invitations extended to eligible adult ITP patients 2. Informed consent obtained 3. Blood samples (10 mL, ~2 teaspoonsful) taken during routinely scheduled venepuncture
2	ITP Study Office Rm 405, Pathology & Pharmacy Building	1. ITP-related information extracted from participant medical records 2. Communication and coordination with collaborating study centres 3. Data collection, entry, and storage 4. Data analysis
3	Molecular Haematology Laboratory Institute of Cell and Molecular Studies	1. DNA & RNA extraction from blood samples 2. Single nucleotide polymorphism (SNP) sequencing within select genes 3. Genome-wide gene expression microarray

12. Who is the Principal Investigator or Local Collaborator for this research at this site?

Title: Forename/Initials: Surname:
 Dr. Drew Provan

Post: Senior Lecturer in Haematology

Qualifications: BSc MBChB DM FRCP FRCPATH

Organisation: Barts and the London, Queen Mary School of Medicine and Dentistry

Work Address: Room 417, Pathology and Pharmacy Building
 Royal London Hospital Telephone: (0)20-3246-0335
 80 Newark Street, London Fax: (0)20-3246-0351

Postcode: E1 2ES Mobile: (0)78-9416-2792

E-mail: a.b.provan@qmul.ac.uk

R&D Only

- a) Will this person interact with research participants, their organs, tissue or data in a way that has a direct bearing on the quality of care? Yes No
- b) Does this person hold a current substantive or honorary contract with the NHS organisation or accepted by the NHS organisation? Yes No

Please provide a copy of the c.v. for the PI.

If an honorary contract is held, a copy of the contract should be submitted, unless previously provided to the R&D office.

14. Give details of all other members of the research team at this site, including academic supervisors and all people who will interact with research participants, their organs, tissue or data in a way that has a direct bearing on the quality of care.

1. Research Member

Title: Forename/Initials: Surname:
 Professor Adrian Newland

Employing organisation: Barts and the London, Queen Mary School of Medicine and Dentistry

Post: Professor of Haematology

Qualifications: MA MBChB FRCP PRCPATH

Role in research team: researcher

R&D Only

- a) Will this person interact with research participants, their organs, tissue or data in a way that has a direct bearing on the quality of care? Yes No
- b) Does this person hold a current substantive or honorary contract with the NHS organisation or accepted by the NHS organisation? Yes No

Please provide a copy of the c.v. for the research team member.

If an honorary contract is held, a copy of the contract should be submitted, unless previously provided to the R&D office.

2. Research Member

Title: Forename/Initials: Surname:

Sister Deborah Kenny

Employing organisation: Barts and the London NHS Trust

Post: ITP Clinical Nurse Specialist

Qualifications: BSc RN

Role in research team: research nurse

R&D Only

- a) Will this person interact with research participants, their organs, tissue or data in a way that has a direct bearing on the quality of care? Yes No
- b) Does this person hold a current substantive or honorary contract with the NHS organisation or accepted by the NHS organisation? Yes No

*Please provide a copy of the c.v. for the research team member.**If an honorary contract is held, a copy of the contract should be submitted, unless previously provided to the R&D office.*

3. Research Member

Title: Forename/Initials: Surname:

Mr. Ameet Sarpatwari

Employing organisation: University of Cambridge

Post: PhD Student, Public Health and Primary Care

Qualifications: BA (Hons) M.Phil

Role in research team: researcher

R&D Only

- a) Will this person interact with research participants, their organs, tissue or data in a way that has a direct bearing on the quality of care? Yes No
- b) Does this person hold a current substantive or honorary contract with the NHS organisation or accepted by the NHS organisation? Yes No

*Please provide a copy of the c.v. for the research team member.**If an honorary contract is held, a copy of the contract should be submitted, unless previously provided to the R&D office.*

4. Research Member

Title: Forename/Initials: Surname:
 Dr Yu–mei Chang
 Employing organisation: Barts and the London, Queen Mary School of Medicine and Dentistry
 Post: Data Manager
 Qualifications: BSc MSc PhD
 Role in research team: researcher

R&D Only

- a) Will this person interact with research participants, their organs, tissue or data in a way that has a direct bearing on the quality of care? Yes No
- b) Does this person hold a current substantive or honorary contract with the NHS organisation or accepted by the NHS organisation? Yes No

Please provide a copy of the c.v. for the research team member.

If an honorary contract is held, a copy of the contract should be submitted, unless previously provided to the R&D office.

15. Does the Principal Investigator or any other member of the site research team 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 further details:

In 2005, the chief investigator served as the Medicines Development Centre (MDC)–Oncology Director at GSK. He still holds the initial volume of company shares (< £ 5,000) he was provided upon starting this position. The chief investigator additionally serves as a member of the ITP Support Association Advisory Board with Professor Adrian Newland.

In 2006, Mr. Ameet Sarpatwari, the study coordinator, was employed by GSK Worldwide Epidemiology as a summer student and subsequently as an independent contractor.

These past and present ties are not believed to pose a potential conflict of interest.

16. What is the proposed local start and end date for the research at this site?

Start date: 01/05/2007 (dd/mm/yyyy)
 Duration (Months): 120
 End date: 01/05/2017 (dd/mm/yyyy)

17. Summary of the research (populated from A10–1)

Purpose:

This study seeks to uncover information regarding the burden, natural progression, treatment effectiveness, and co–morbidity of adult ITP in the United Kingdom via establishment of a multi–centre disease registry.

Background:

A previous version of this study was submitted to the London Multi–centre Research Ethics Committee (MREC) in 2002 under the title, “Establishment of a UK Registry for Adults with Idiopathic Thrombocytopenic Purpura (ITP) and

Investigation into the Role of Cytokine Genes.” The proposed study was ethically approved in August 2002 (MREC/02/2/58) and remained active until August 2005, during which time over 600 patients were enrolled.

However, due to unforeseen circumstances resulting in a switch of positions, the chief investigator was forced to limit further investigation and analysis on this cohort at that time. He has since returned to the Royal London Hospital as both a senior clinical lecturer and consultant haematologist and is eager to reinitiate the study with minor substantive alterations. He will be aided in this task by a study coordinator, a molecular scientist, and a data manager, full-time positions funded through support from GlakoSmithKline Inc. and The ITP Support Association.

Design & Methodology:

Recruitment & Consent:

The proposed protocol entails investigations into both prospective and past study participants. Within haematology clinics at collaborating centres, adult patients presenting with low platelet counts ($< 150 \times 10^9$ platelets/L) and exhibiting no evidence of other underlying thrombocytopenic (low-platelet) diseases following a standard ITP workup will be invited to take part in the investigation.

This recruitment process will be directed by the study coordinator. Consent forms and information sheets will be electronically downloaded from the secure study server by local collaborating haematologists, who will discuss their content with study invitees. Potential participants will additionally have the opportunity to discuss questions or concerns with members of the chief investigator's team via telephone. Written consent will be taken and stored at locally, with copies of the agreement forwarded to both the study data manger and the study participant.

Blood Collection & Genetic Testing:

At the time of registration, one blood sample (10 ml, ~2 teaspoonsful) will be drawn during a routinely scheduled venepuncture and mailed to the study coordinator, who will be responsible for its semi-anonymisation via labeling with uniquely allocated participant and centre reference numbers. The sample will then be forwarded to the Molecular Haematology Laboratory at The Royal London Hospital, where its genetic contents will be isolated and stored for subsequent single-nucleotide polymorphism (SNP) and gene expression analysis.

We will use polymerase chain reaction (PCR) technology to amplify DNA regions of genes hypothesised to be linked with ITP and other autoimmune diseases. As illustrated in Table 1, the presence of SNPs within genes coding for IL-1(alpha), IL-2, IL-4, IL-4R, IL-6, IL-8, IL-10, TGF-(beta), TNF-(alpha), IFN-(gamma), Fc(gamma)RII & III, CTLA-4, NRAMP-1, CTLA-4, and GAL-2 will be recorded and assessed for their ability to predict disease severity and patient response to treatments.

Table 1: Genes for SNP Testing

Genes	Citation
IL-1(alpha)	McDowell et al., 1995
IL-2	John et al., 1998
IL-4	Cantagrel et al., 1999
IL-4R	Hackstein et al., 1999
IL-6	Fishman et al., 1998 Olomolaiye et al., 1998
IL-8	Bornscheuer et al., 1999
IL-10 (x 3)	Turner et al., 1997
TGF-(beta) (x 2)	Lympany et al., 1998
TNF-(alpha)	Wilson et al., 1997
IFN-(gamma)	Siegmund et al., 1998
Fc(gamma)RII & III	Jiang et al., 2000
NRAMP-1	Singal et al., 2000
CTLA-4	Heward et al., 1999
GAL-2	Liu et al., 2001

Table 1 Legend: IL, interleukin; TGF, transforming growth factor
TNF, tumour necrosis factor; IFN, interferon; CTLA, cytotoxic T
lymphocyte antigen; Fc(gamma)R, Fc(gamma)receptor; NRAMP, natural
resistance associated macrophage protein; GAL, galactose permease;
(x n), number of polymorphisms within gene.

Gene expression will be measured using microarrays, which contain hundreds of genes known to be important in the

normal functioning of the cell and in the development of diseases like cancer and autoimmunity. These arrays allow us to take a snapshot of gene expression at a particular time in a particular cell type, snapshots that we can subsequently compare to see if particular genes are involved in the disease process. The data gathered will permit analysis of the relationship between different genes and the disease process. The development of novel therapies may be possible by our increased understanding of the genes crucial to the development ITP.

Medical Record Extraction Procedure:

During the defined ten-year study period, information on the following fields will be extracted from patient hospital records at registration, six-months following registration, and annually following registration using standard proforma. For study participants registered at The Royal London Hospital, these extractions will be undertaken by a three-person team comprising the study coordinator, the data manager, and a data specialist. Data pertaining to the aforementioned fields will be doubly entered into the electronic study database and cross-verified. Should inconsistencies arise during this check, the double extraction protocol will be repeated. At all other collaborating centres, local haematologists will be responsible for performing scheduled extractions and for forwarding the abstracted data to the chief investigator's team using a secured server.

Fields for Extraction:

Demographic Information: [Registration Form Only]

- Patient name
- Patient gender
- Patient date of birth
- Patient mailing address
- Consultant haematologist name
- Centre name
- Centre address
- Date of registration

Main ITP Information:

- Date of diagnosis [(Re-)Registration Forms Only]
- Platelets (count & date)
- Change of Diagnosis (yes/no) [1st Annual/Re-Registration Form Only]

Treatment: (yes/no; date, dosage & duration where applicable)

- Prednisolone
- IVIg
- Splenectomy (laparoscopic/standard technique)
- Anti-D
- Cyclic high-dose methylprednisolone
- Dexamethasone
- Danazol
- Azathioprine
- Cyclophosphamide
- Vinca alkaloids
- Mycophenolate
- Plasmapheresis/protein A immunoadsorption
- Interferon
- Cyclosporine
- Rituximab
- Platelet transfusion
- Red blood cell transfusion
- H. pylori treatment

Co-Morbid Conditions: (yes/no, date)

- Cataracts
- Long-bone fractures
- Type II diabetes
- Hypertension
- Peptic ulcers
- H. pylori infection
- Chronic renal failure or impairment
- Chronic liver disease
- Myocardial infarction

- Hepatitis C
- Splenomegaly
- Thyroid disease
- Depression/anxiety
- Miscarriage
- Cushing's syndrome
- Candida infections
- Pneumonia
- Mortality

Biochemical Fields (levels at diagnosis) [(Re-)Registration Only]

- Alanine transaminase
- Aspartate transaminase
- Alkaline phosphatase
- Bilirubin

Haematological Fields [(Re-)Registration Form Only]

- Haemoglobin (levels at diagnosis)
- White blood cells (levels at diagnosis)
- Blood group (A, B, AB & O; positive/negative)
- Marrow aspirate (yes/no, normal/abnormal at diagnosis)
- Trepchine biopsy (yes/no, normal/abnormal at diagnosis)
- Direct agglutination test (positive/negative at diagnosis)

Immunological Fields [(Re-)Registration Form Only]

- Immunoglobulin (levels at diagnosis)
 - o IgA
 - o IgM
 - o IgG
- Anti-nuclear antibodies (levels at diagnosis)
- Autoantibody screen (positive/negative at diagnosis)

Coagulatory Fields (levels at diagnosis) [(Re-)Registration Form Only]

- Prothrombin time
- Activated partial prothrombin time
- Lupus anticoagulant
- Anticardiolipin antibody

Indium Scanning (48 hour spleen/liver ratio, date)

Bleeding Events: (yes/no, date, severity)

- cutaneous bleeds
- bleeds from the oral cavity
- epistaxis
- menorrhagia
- haematuria
- gastrointestinal bleeds
- intracranial haemorrhage
- muscle bleeds
- joint bleeds

Past Study Participants:

Death registries in England, Scotland, Wales, and Northern Ireland will be scanned to assess the status of past study participants. Living individuals from this cohort will be sent a mailing highlighting the substantive alterations to the study and providing a written means to opt out from further retrospective and prospective investigation. Blood samples will not be requested from these patients. However, the same fields of information will be extracted from their hospital records as from the records of prospectively enrolled study participants. These extractions will be performed by either the three-person team or local collaborating haematologists at the time of re-registration, defined as two weeks following the post-marked date of the study update mailing, and annually thereafter during the defined ten-year study period.

Medical Record Extraction Analysis:

Abstracted information from participant medical records will be used to conduct the qualitative and quantitative analyses highlighted in Appendix A1, which include estimations the burden of adult ITP in the United Kingdom, the natural progression of the disease, and the effectiveness of currently implemented therapies. These analyses will be conducted half-way through the study and at its conclusion in 2017; results from these investigations will be published in our monthly study newsletter and in The Platelet, the official newsletter of the ITP Support Organisation.

Communication of Study Progress:

Though study participants will not be actively involved in the investigation following registration, they will be kept closely apprised of study progress through a mailed and electronically posted monthly newsletter. They, too, will be provided with multiple means to contact the chief investigator's team regarding any questions or concerns throughout the duration of the study.

References:

- 1) T. L. McDowell, J. A. Symons, R. Ploski, O. Forre, G. W. Duff, Arthritis Rheum 38, 221–8 (1995)
- 2) S. John, et al., Annals Of The Rheumatic Diseases 57, 361–5 (1998)
- 3) A. Cantagrel, et al., Arthritis Rheum 42, 1093–100 (1999)
- 4) H. Hackstein, H. Kluter, L. Fricke, J. Hoyer, G. Bein, Tissue Antigens 54, 471–7(1999)
- 5) D. Fishman, et al., J Clin Invest 102, 1369–76 (1998)
- 6) O. Olomolaiye, N. A. Wood, J. L. Bidwell, Eur J Immunogenet 25, 267 (1998)
- 7) E. Bornscheuer, D. Zillikens, J. M. Schroder, M. Sticherling, Dermatology 198, 118–121 (1999)
- 8) D. M. Turner, et al., Eur J Immunogenet 24, 1–8 (1997)
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- 10) A. G. Wilson, J. A. Symons, T. L. McDowell, H. O. McDevitt, G. W. Duff, Proc Natl Acad Sci USA 94, 3195–9 (1997)
- 11) T. Siegmund, et al., Thyroid 8, 1013–7 (1998)
- 12) Y. Jiang, et al., Immunogenetics 51, 429–35 (2000)
- 13) D. P. Singal, J. Li, Y. Zhu, G. Zhang, Tissue Antigens 55, 44–7 (2000)
- 14) J. M. Heward, et al., J Clin Endocrinol Metab 84, 2398–401 (1999)
- 15) H. X. Liu, et al., Proc Natl Acad Sci USA 98, 9960–9964 (2001)

18. Details of clinical interventions (populated from A12 where enabled)

Additional Intervention	Average number per participant		Average time taken	Details of additional intervention or procedure, who will undertake it, and what training they have received.
	Routine Care	Research		
Venepuncture	> 1	1	Once at enrollment	One sample of blood (10 mL, ~2 teaspoonsful) will be taken from consenting study participants during a routinely scheduled venepuncture for platelet count analysis at outpatient clinics.

19. Details of non-clinical interventions (populated from A13 where enabled)

Additional Intervention	Average number per participant	Anticipated average time taken	Details of additional intervention or procedure, who will undertake it, and what training they have received.

20. Will any aspects of the research at this site be conducted in a different way to that described in Parts A and B or the study protocol?

Yes No

If Yes, explain and give reasons.

21. How many research participants/samples is it expected will be recruited/obtained from this site?

Based upon recruitment numbers seen in a previous version of this study, it is expected that approximately 325–375 participants will be successfully recruited from The Royal London Hospital over the proposed ten year investigation.

22. Give details of how potential participants will be identified locally and who will be making the first approach to them to take part in the study?

Adult patients at the Knutsford Clinic presenting with low platelet counts ($< 150 \times 10^9/L$) and exhibiting no evidence of other underlying thrombocytopenic (low-platelet) diseases following a standard ITP workup will be invited by either Dr. Provan or Professor Newland to take part in the investigation.

23. Who will be responsible for obtaining informed consent at this site? What expertise and training do these persons have in obtaining consent for research purposes?

1 <input checked="" type="checkbox"/>	Dr. Drew Provan	Dr. Provan will serve as chief investigator for the proposed study and is an internationally recognised expert on adult ITP. He has extensive experience conducting observational research and obtaining informed consent. Dr. Provan has attend a Barts and the London NHS Trust Research Governance Session on the 3rd of May.
2 <input checked="" type="checkbox"/>	Professor Adrian Newland	Professor Newland is a named investigator for the study and an internationally recognised expert on adult ITP. He has extensive experience conducting observational research and obtaining informed consent. Professor Newland has recently attended a Barts and the London NHS Trust Research Governance Session.
3 <input checked="" type="checkbox"/>	Sister Deborah Kenny	Sister Deborah Kenny is an ITP clinical nurse specialist. She has extensive experience conducting observational research, obtaining informed consent, and counseling patients with chronic disease. Sister Kenny has recently attended a Barts and the London NHS Trust Research Governance Session.
4 <input type="checkbox"/>	Mr. Ameet Sarpatwari	
5 <input type="checkbox"/>	Dr Yu–mei Chang	

27. Is there a contact point where potential participants can seek independent advice about participating in the study?

Yes. Potential participants may seek independent advice about participating in the study from the ITP Support Association, the principal support group for ITP patients in the United Kingdom. Contact information for this group has been provided on study overview documents that will be provided to potential participants. All inquiries submitted to the support group will be fielded by individuals with no involvement in the proposed study.

R&D Only

28. Please provide a copy on headed paper of the participant information sheet and consent form that will be used locally. This must be the same generic version submitted to/approved by the main REC for the study while including relevant local information about the site, investigator and contact points for participants (see guidance notes).

If you consider that changes should be made to the generic content of the information sheet to reflect site-specific issues in the conduct of the study (see 20), give details below. A substantial amendment may need to be discussed with the Chief Investigator and submitted to the main REC.

29. 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)

Where English is not the eligible patient's first language, recruitment will only take place following discussion through an interpreter. At The Royal London Hospital, the Advocates (interpreters) Department liaises closely with clinicians; advocates routinely attend our clinics to explain diagnoses and possible treatments, and we will seek their help in explaining the study details to patients whose first language is not English. We will ask that collaborators at other centres employ interpreters as required.

What local arrangements have been made to meet these requirements (where applicable)? Local arrangements are detailed above.

30. What arrangements will be made to inform the GP or other health care professionals responsible for the care of the participants?

Dr. Provan, Sister Kenny, and Professor Newland will be responsible for the routine care of study participants at The Royal London Hospital. As a result, no further arrangements will be made to inform the clinical care team of patient involvement in the study save for a note placed in each participant's hospital record.

33. What arrangements (e.g. facilities, staffing, psychosocial support, emergency procedures) will be in place at the site, where appropriate, to minimise the risks to participants and staff and deal with the consequences of any harm?

The proposed study poses no additional risk of pain or discomfort beyond that resulting from routine care. Therefore, no additional arrangements will be made to deal with the consequences of any harm.

R&D Only

35. What are the arrangements for the supervision of the conduct of the research at this site? Give name and contact details of any supervisor not already listed in the application.

The chief investigator has formed a five-member UK Adult ITP Registry Monitoring Committee (UKAIRMC), which will be charged with tracking recruitment rates, monitoring collected data, and auditing medical record extraction, blood sample procurement, and data protection methods. This committee will convene yearly and report its findings to the Joint Research Office for Barts and the London NHS Trust and Barts and the London, Queen Mary's School of Medicine and Dentistry.

R&D Only

37. Will any external funding be provided for the research at this site?

Yes No

If Yes, indicate the source and details of the funding:

1. Source: GlaxoSmithKline Research Development Ltd.	
Type of funding	Details (including breakdown over years if appropriate)
(i) Block grant	The principal investigator has signed a research agreement with GlaxoSmithKline providing £267,875 in funds to support the UK Adult ITP Registry over a two year period. A second proposal to expand the study will be submitted at this time.
(ii) Per participant	
(iii) Other (give details)	

2. Source: ITP Support Association	
Type of funding	Details (including breakdown over years if appropriate)
(i) Block grant	The principal investigator has received a one-year, £40,000 grant from the ITP Support Association to fund a post-doctoral fellowship entailing oversight of genetic investigations of adult ITP.
(ii) Per participant	
(iii) Other (give details)	

R&D Only

38. Which organisation will receive and manage this funding?

This funding will be placed in the principal investigator's research account with Barts and the London, Queen Mary's School of Medicine and Dentistry and will be managed by the university's finance department.

R&D Only

39. Authorisations required prior to R&D approval

This section deals with authorisations by managers within the NHS organisation. It should be signed in accordance with the guidance provided by the NHS organisation. This may include authorisation by line managers, service managers, support department managers, pharmacy, data protection officers or finance managers, depending on the nature of the research. Managers completing this section should confirm in the text what the authorisation means, in accordance with the guidance provided by the NHS organisation. This section may also be used by university employers or research staff to provide authorisation to NHS organisations, in accordance with guidance from the university.

1. Type of authorisation:

Signature:

Date:

Title: Forename/Initials: Surname:

Organisation:

Post:

Work Address:

Telephone:

Fax:

Postcode:

Mobile:

E-mail:

Declarations

Declaration by Principal Investigator or Local Collaborator

1. The information in this form is accurate to the best of my knowledge and I take full responsibility for it.
2. I undertake to abide by the ethical principles underpinning the World Medical Association's Declaration of Helsinki and relevant good practice guidelines in the conduct of research.
3. If the research is approved by the main REC and NHS organisation, I undertake to adhere to the study protocol, the terms of the application of which the main REC has given a favourable opinion and the conditions requested by the NHS organisation, and to inform the NHS organisation within local timelines of any subsequent amendments to the protocol.
4. If the research is approved, I undertake to abide by the principles of the Research Governance Framework for Health and Social Care.
5. I am aware of my responsibility to be up to date and comply with the requirements of the law and relevant guidelines relating to the conduct of research.
6. I undertake to disclose any conflicts of interest that may arise during the course of this research, and take responsibility for ensuring that all staff involved in the research are aware of their responsibilities to disclose conflicts of interest.
7. I understand and agree that study files, documents, research records and data may be subject to inspection by the NHS organisation, the sponsor or an independent body for monitoring, audit and inspection purposes.
8. I take responsibility for ensuring that staff involved in the research at this site hold appropriate contracts for the duration of the research, are familiar with the Research Governance Framework, the NHS organisation's Data Protection Policy and all other relevant policies and guidelines, and are appropriately trained and experienced.
9. I undertake to complete any interim and/or final reports as requested by the NHS organisation and understand that continuation of permission to conduct research within the NHS organisation is dependent on satisfactory completion of such reports.
10. I undertake to maintain a project file for this research in accordance with the NHS organisation's policy.
11. I take responsibility for ensuring that all serious adverse events are handled within the NHS organisation's policy for reporting and handling of adverse events.
12. I understand that information relating to this research, and about me as a researcher, will be held by the R&D office and may be held on national research information systems, and that this will be managed according to the principles established in the Data Protection Act 1998.
13. I understand that the information contained in this application, any supporting documentation and all correspondence with the R&D office and/or the REC system relating to the application will be subject to the provisions of the Freedom of Information Acts and may be disclosed in response to requests made under the Acts except where statutory exemptions apply.
14. I understand that information relating to this research (including my contact details) may be publicly available through the National Research Register.

Signature of Principal Investigator
or Local Collaborator:

Print Name: Dr. Drew Provan

Date: 03/07/2007