

UKITP REGISTRY STUDY PROTOCOL 2.5



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Full Title	United Kingdom Adult Idiopathic Thrombocytopenic Purpura (ITP) Registry: An Investigation of Disease Progression, Treatment Effectiveness, and Co-morbid Conditions
Short Title/Acronym	UK ITP Registry
Sponsor	Barts Health Joint Research Management Office 5 Walden Street London E1 2EF Phone: 020 7882 7260 Email: research.governance@qmul.ac.uk
REC Reference	07/H0718/57
Sponsor reference or ReDA	005148
IRAS Project ID	92703
Chief Investigators	Dr Vickie McDonald

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GP	General Practitioner
HSCIC	Health and Social Care Information Centre
ITP	Immune Thrombocytopenia
JRMO	Joint Research Manage Office for Barts Health Trust and Queen Mary University of London
MREC	London Research Ethics Committee
NHS	National Health Service
NICE	National Institute for Health and Care Excellence
RLH	Royal London Hospital (is part of Barts Health Trust)
SNP	Single Nucleotide Polymorphism

3 SIGNATURE PAGE

Chief Investigator Agreement

The clinical study as detailed within this research protocol (**UKITPR Study Protocol 2.5, dated 28th January 2020**), or any subsequent amendments will be conducted in accordance with the Research Governance Framework for Health & Social Care (2005), the World Medical Association Declaration of Helsinki (1996) and the current applicable regulatory requirements and any subsequent amendments of the appropriate regulations.

Chief Investigator Name: Dr Vickie McDonald

Chief Investigator Site: Barts Health NHS Trust

Signature and Date:

Sub-Investigator (responsible for the Pregnancy Registry) Name: Dr Sue Robinson

Sub-Investigator Site: Guy's and St Thomas' NHS Foundation Trust

Signature and Date:

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4 Summary of Study

This study seeks to uncover information regarding the aetiology, epidemiology, natural progression¹, treatment effectiveness, and co-morbidities of adult ITP in the United Kingdom via a multi-centre disease registry.

Short Title	UKITP registry
Methodology	A UK-wide registry of patients with ITP
Research Sites	Barts Health NHS Trust and Queen Mary, University of London with other NHS Trusts as data collection centres
Objectives/Aims	To better understand the causes, treatment responses and outcomes in patients with ITP
Number of Participants/Patients	No restriction – open to all patients in the UK with ITP who fit the eligibility criteria
Main Inclusion Criteria	Adults (age >18 years) with primary ITP or pregnancy-associated primary ITP
Main Exclusion Criteria	Secondary ITP, patients <18years of age, patients unwilling or unable to consent
Statistical Methodology and Analysis (if applicable)	N/A
Proposed Start Date	Commenced 2007 (REC 07/H0718/57) Previous Substantial Amendment (5 - 12/06/2017) Current amendment start date: 12 th June 2018
Proposed End Date	30 th June 2023

¹ Natural progression shall be defined as platelet count, bleeding events, and mortality over time.

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5 Introduction

Primary Immune Thrombocytopenia (ITP) is a rare bleeding diathesis, characterized by a platelet count $<100 \times 10^9/L$ with an autoimmune aetiology.

It is a complex heterogeneous disease, the clinical features, severity and current treatment practices vary considerably^{1, 2, and 3}. In order to identify subgroups or clusters of patients with shared attributes or outcomes a large study cohort is required. This will also allow the generation of statistically meaningful as well as valid and reliable research findings.

The UK ITP Registry aims to collect data in order to understand the epidemiology, aetiology, prognosis, treatment and outcomes of people with primary ITP. The present extension of the Registry sets out to occupy a central position in primary ITP research and fill the gaps in existing literature by assessing the development of ITP throughout all stages of adult life.

This extension adds a new subgroup: the prospective data collection regarding the management and outcome of pregnancy in patients with ITP to further our understanding of the epidemiology of ITP in pregnancy, pregnancy outcome and provide a prospective tool to guide evidence based consistent practice. The pregnancy ITP section will have Dr Sue Robinson Consultant Haematologist at Guy's and St Thomas' NHS Foundation Trust, as sub-investigator. Dr Robinson will handle any clinical enquiries which are relevant for this part of the Registry. All contact details are provided on the Registry website and at the end of this protocol.

6 Study Objectives

6.1 Primary Objectives:

To collect clinical information and biological samples from participants with primary ITP in order to investigate its epidemiology, aetiology, prognosis, treatments and outcomes throughout all stages of adult life (including pregnancy).

6.2 Secondary Objectives:

To investigate genetic associations with epidemiology, aetiology, prognosis, treatment effectiveness and outcomes in primary ITP

To investigate factors influencing response in platelet counts in primary ITP.

7 Methodology

7.1 Inclusion Criteria

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- *Patient with platelet count of $<100 \times 10^9/L$ and no evidence of other known thrombocytopenic inducing drugs or disease i.e. diagnosis of **primary ITP***
- *Patients aged 18 and over living in the UK*
- *Patients able to give informed consent*

**Patients who have previously been diagnosed with primary ITP which has resolved can still be included if retrospective data from the period of active ITP disease can be collected.*

7.2 Exclusion Criteria

- *Patients not meeting the inclusion criteria*
- *Patient unwilling or unable to give consent*
- *Secondary ITP from any cause (except pregnancy ITP)*

8 Study Design

This study is a registry. As with previous versions of the protocol, the study will entail investigation of prospective and past study participants. Any patients who were diagnosed with ITP at any time will continue to be enrolled onto the registry, providing data from the period of active ITP can be obtained (please see Study Scheme Diagram below).

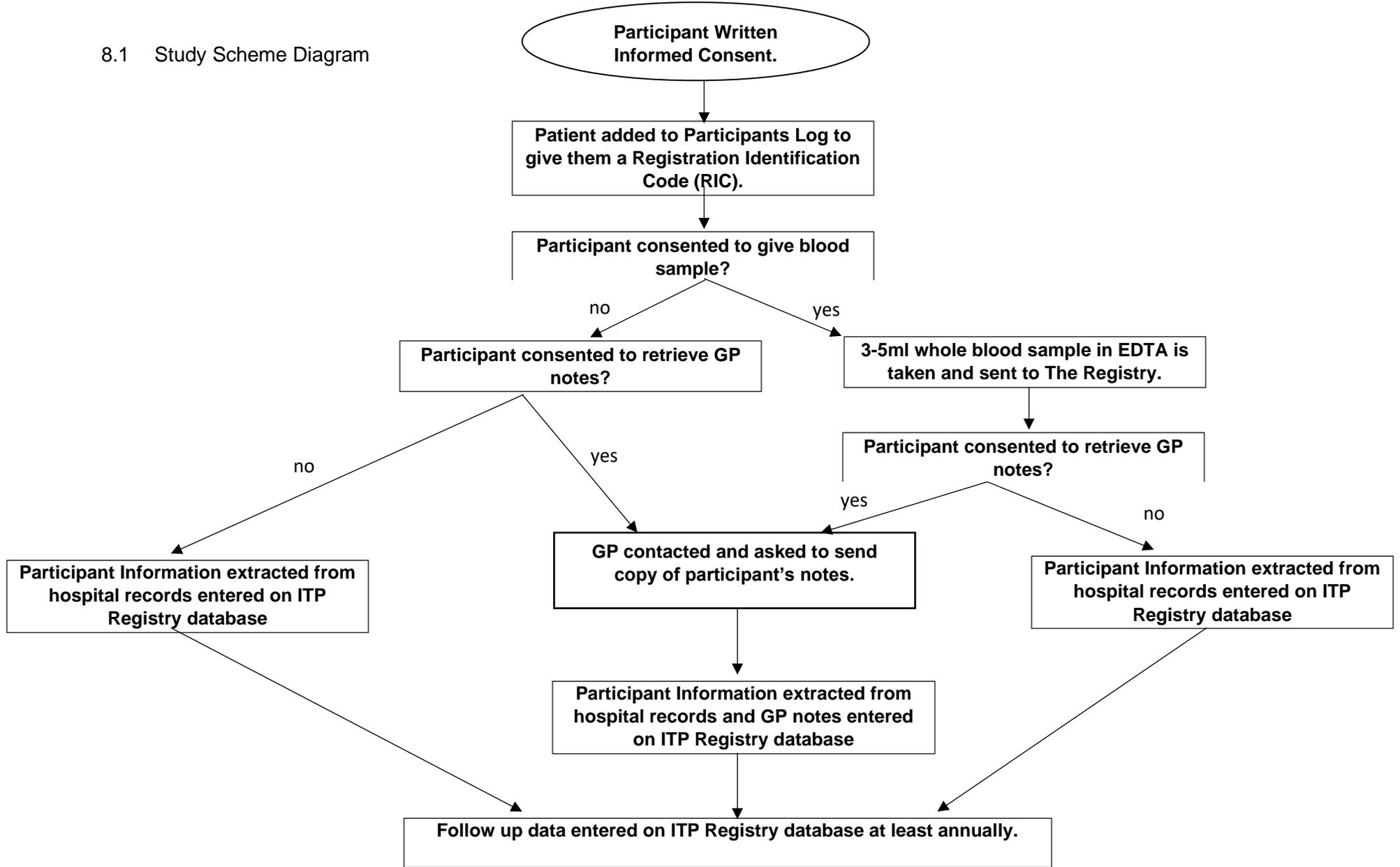
The UK ITP Registry is designed to collect longitudinal epidemiological data as well as collect blood sample for genetic analysis. Patients who are eligible for the study are identified by the local Principle Investigator's delegated team and consented locally. If the participant consents to donating a blood sample, a 4-8ml EDTA blood sample will be taken by the local team and sent to the ITP Registry. The local teams are responsible for extracting participant data from both hospital and GP medical notes and adding this information to the Registry database. Follow up information on the participant should be obtained at least annually and added to the database.

The registry has been extended to collect data on ITP during pregnancy. Pregnancy data will be collected alongside non-pregnancy ITP-related data in two separate databases.

The UK ITP Registry will use the data collected locally to analyse patterns in the UK ITP population. Blood samples are used to extract DNA which is stored for future genetic analysis. Analyses will be run at different time points throughout the lifespan of the Registry. Data quality checks will be run regularly and the site will be expected to help with data queries.

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8.1 Study Scheme Diagram



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9. STUDY PROCEDURES

9.1 Informed Consent Procedure

Adult patients presenting at haematology clinics or within collaborating centres with a low platelet count ($< 100 \times 10^9 /L$) and no evidence of known thrombocytopenic-inducing disease or treatments following a standard ITP workup will be invited to take part in the study.

Identified eligible adult patients should be given the Prospective Participants Overview 3.2 to familiarise themselves with the study and given at least 24 hours to review and ask questions before entering the study. Consent should be taken using ITPR Study Informed Consent Agreement 4.4 and ITPR Pregnancy Study Informed Consent Agreement 1.0.

The consent asks participants to agree to the following points:

1. To be part of the Registry
2. For information to be extracted from their medical notes
3. For the site team to obtain information from other sources including:
 - a. Summary Care Records
 - b. General Practitioner notes
 - c. Data Linkage Services provided by the NHS's Health and Social Care Information Centre
4. To donate 4-8ml of blood for genetic studies into ITP
5. For pregnant participants only: collection of data on the management of ITP during pregnancy and the outcome of a participants' pregnancy.

9.2 Anonymisation of patient

Following consent, the participant will be added to the site's Participants' Log. This will assign them a UK ITP Registry Identification Code (RIC) which is used to add the clinical details to the database anonymously.

Following entry of each new participant, a copy of the consent form and the updated Participants Log should be sent securely to the registry data manager via the registry nhs.net email account or post. This is stored securely and separately from participant clinical data to ensure anonymisation of clinical data.

9.3 Funding for recruitment

This study is registered with the UK CRN portfolio. Sites are allocated NIHR funding proportional to the number of new participants they have recruited that year. The registry requires a copy of the consent form and updated Participants Log for each new recruit in order to include them in the site NIHR funding returns.

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9.4 Blood Collection for Genetic Analysis, Blood Cell Analysis and Immune Profiling

9.4.1 Samples for genetic analysis

Following registration, a single 4-8ml blood sample in a generic EDTA tube will be drawn. The sample does not have to be taken at the time of consent but as close to this time as possible. The sample should be clearly labeled with the patient RIC as well as the date of venepuncture. The sample should then be sent to:

Mr Sean Platton
The UK ITP Registry C/O Haematology Laboratory
4th Floor
Pathology and Pharmacy Building
Royal London Hospital
80 Newark Street
E1 2EH

Blood Samples will be used to isolate the genetic materials which will be used to analyse for factors involved in the development of ITP as well as disease severity and progression. Genetic contents will be isolated and stored for subsequent single-nucleotide polymorphism (SNP) and gene expression analysis. Polymerase chain reaction (PCR) or other contemporary genetic technology will be used to amplify DNA regions of genes hypothesised to be linked with ITP or other autoimmune diseases. The presence of SNPs within genes will be recorded and assessed for their ability to predict disease severity and patient response to treatments. Genome-wide gene expression will be measured using state of the art microarray technology, which will permit snapshots of expression at a particular time in a particular cell type. These expression profiles will be used as an early, hypothesis-generating tool to gauge whether novel genes may be involved in the disease process.

9.4.2 Sub-study- Platelet and Immunological Investigation

A subset of participants from The Royal London Hospital will be invited to take part in a sub-study looking at platelet functionality and immunological profiling.

These participants will be invited to contribute up to of 50mls (10 teaspoons) over a six month period. Existing registry patients or those who have expressed an interest in participating will be given the patient information leaflet with a verbal explanation of the sub-study. Donations will be obtained at a subsequent routine visit when the participants have had chance to consider their involvement in the study.

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The samples will be used for analysis of antiplatelet antibodies, leucocyte surface markers, leucocyte (in particular B and T cell) functional assays, autoantibody analysis and analysis of gene and protein expression. Any new relevant assays for ITP or autoimmune disease will also be used.

In addition to participants with ITP, a group of gender and age matched volunteers will be recruited for data comparison. The inclusion criteria for this non-ITP control group will be:

- Adult (≥ 18 years) patients without a diagnosis of ITP
- No thrombocytopenia or autoimmune disease

Note: Guidance on sample collection, storage and transfer, including dispatch addresses, are described in appendix 1.

9.5 Data Collection

Once a new participant has consented to be part of the registry, the site should use their medical notes and local electronic systems to extract ITP-related information, using the ITPR Initial Data Collection Sheet UK 2.5 to guide data entry. A new record must be created for each new participant on The ITP Registry Database using their RIC. We advise that Initial data entry is done within six weeks of consent.

Follow up data collection can be guided by UKITP Follow-up Information Sheet 1.9. Follow-up of participants should be done at least annually. Participants are not required to come in for follow-up data collection. Appendix 2 should be used when entering ITP treatment to ensure doses are given in the correct units. Appendix 3 specifies time periods in which platelet counts are required relative to treatments. This should be used to collect participant's platelet counts.

9.5.1 General Practitioner (GP) Notes

Although we expect that most information that we require will be available from the medical records at the referral hospital (i.e. collaborating centre), on certain occasions some may not be available. To overcome these gaps in data, GP notes should be requested. ITPR General Practitioner Letter template UK 1.2 and ITPR GP Proforma (Data Collection Sheet) UK 1.2 along with a copy of the patient consent form should be sent to the participant's GP. Once the medical notes are received back, the site team should use the ITPR Initial Data Collection Sheet UK 2.5 to extract the relevant ITP-related information and add this to the registry Database. Please note that GP practices should send participant notes to the site team instead of via the Registry as was the case in previous versions.

9.5.2 Fields for extraction from medical and other related-records

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Data will be collected using the following headings (more detail can be found on the data collection forms; Initial Data Collection Sheet UK 2.5 and Follow-up Information Sheet 1.9):

Headings for extraction
Demographic, anthropometric and lifestyle information
Referral centre information
Bleeding Events
ITP Treatments
Co-therapies
Co-Morbid Conditions
Family Disease History
Blood counts- including biochemistry and coagulation fields
Diagnostic Information
Mortality
Adverse events and related information

9.6 ITP during Pregnancy

Extension of the ITP Registry to include ongoing, prospective data collection regarding the management and outcome of pregnancy in patients with ITP will further our understanding of the epidemiology of ITP in pregnancy, pregnancy outcome and provide a prospective tool to guide evidence based consistent practice.

Pregnant women who meet the following criteria will be invited to take part in the pregnancy sub-study:

- Primary immune thrombocytopenia diagnosed prior to pregnancy.
- Primary immune thrombocytopenia diagnosed in pregnancy where:

the platelet count falls to $<50 \times 10^9/L$

OR

treatment for ITP is required during pregnancy or up to 3 months post-partum.

Participants should be consented for the pregnancy registry in addition to the main registry (i.e. separate consents). Identified eligible participants should be given the UK ITP Pregnancy registry Prospective Patient overview v1.0. If they agree to participate they should sign the ITP Pregnancy Study informed consent agreement v 1.0.

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Participants may be looked after by a different team or hospital during their pregnancy. The medical notes and maternity note for these patients should be requested for data extraction. ITPR Pregnancy Registration Sheet 1.0 and ITPR Pregnancy Status and Outcome Sheet 1.0 can be used to guide data extraction.

Please note that this part of the Registry will be led jointly by Dr Sue Robinson, Consultant Haematologist of Guy's and St Thomas' NHS Foundation Trust, and the Chief Investigator the Registry team. Dr Sue Robinson has a specific interest in obstetric haematology and will handle any clinical enquiries which are relevant for this part of the Registry. All contact details are provided on the Registry website and at the end of this protocol.

9.6.1 Fields for extraction for ITP during pregnancy

Data will be collected using the following headings (more detail can be found on the data collection forms; Pregnancy Registration Sheet 1.0 and Pregnancy Status and Outcome Sheet 1.0):

Headings for extraction
Additional fields to be collected for the pregnancy section of the Registry are shown below:
Additional Demographic Details
Obstetric History
Details of current pregnancy
Treatment in Pregnancy
Blood counts- including biochemistry and coagulation fields
Details of delivery
Details of infant outcome

9.7 Data Capture

Appendices 2 and 3 should be used to guide data entry as they specify units required for ITP treatment doses and minimum timing of required platelet counts relative to treatment.

The Registry team will be responsible for reviewing the quality and completeness of the data regularly. Any unusual or missing values will be sent back to the centre to be checked against local medical records.

9.8 Subject Withdrawal

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Patients are free to withdraw from the Registry at any time. Their site team should inform the ITP Registry team so that their data can be removed.

If a cause of participant's thrombocytopenia is found, so that ITP is no longer the lead diagnosis, the registry team must be contacted so that the participant's data can be removed.

9.9 End of Study Definition

The study recruitment has been extended to 30th June 2022 and so the new study end date will be 30th June 2023.

9.10 Statistical Consideration

Standard Statistical methods will be used to analyse data with the assistance of standard statistical software.

10 ETHICS

The Principal Investigator is responsible for ensuring that the study will be carried out in accordance with the ethical principles in the Research Governance Framework for Health and Social Care, Second Edition, 2005 and its subsequent amendments as applicable to legal and regulatory requirements.

10.1 Safety Considerations

As a data collection centre, participants' safety is not at risk by being in the study. The usual phlebotomy risks apply to taking a blood sample.

10.2 Past Study Participants

Owing to the non-sensitive nature of the proposed revisions, the London MREC (03/07/2007 - 07/H0718/57) determined that it would not be necessary to re-consent past study participants. The same information will be extracted from the medical records of past participants as from those of prospectively enrolled participants.

10.3 Data Handling and Record Keeping

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Information relating to participants will be kept confidential and managed in accordance with the GDPR, the Data Protection Act, NHS Caldecott Principles, the Research Governance Framework for Health and Social Care, and the conditions of Research Ethics Committee Approval.

All electronic data is kept securely within restricted access shared drives at Barts Health NHS Trust. Data from the Registry is kept separately from information with patient identifiers. Patient Identifiable information such as Participants Logs are kept encrypted and in their own restricted access drive. The registry keeps this information to monitor patients and avoid duplication as patients may move between sites and to ensure accurate NIHR returns. Only the Chief Investigator's team and the site team can view data from any site.

According to the Research Governance Framework and Trust Policy, records will be kept for 20 years from study closure. For studies involving Bart's Health Trust patients, undertaken by Trust staff, or sponsored by BH or QMUL, the approved repository for long-term storage of local records is the Trust Modern Records Centre. External centres are expected to follow the same records retention time frame.

10.4 Laboratories

Blood samples will be processed at Bart's Health NHS Trust or Queen Mary, University of London campus. Samples will be processed as soon as possible and DNA stored in secure location. All samples received by the Registry should be anonymised and only have the RIC on the label. Received samples will be logged on our central database and on the UK ITP Registry itself. Samples waiting for DNA extraction will be stored in a -20°C freezer until a batch has been collected to undergo DNA extraction. Extracted DNA will be stored in a -20°C/-80°C freezer on trust premises until they need to be used for analysis.

10.5 Indemnity

The Registry is sponsored by Barts Health. The Joint Research Management Office (JRMO) for Bart's Health and QMUL also oversee the research activities within Barts Health Trust. All confidential materials, including all data received from NHS Digital (or HSCIC) and ONS, which are related to the Registry, will remain within Barts Health NHS Trust's secure premises and network. These data will also be processed within Barts Health NHS Trust. Only anonymised data received by the Registry will be analysed, if required, using QMUL facilities.

While we do not expect the participants to suffer any harm as a result of their participation in the study, Barts Health has agreed that if they are harmed as a result of their participation in the study, they will be compensated, provided that, on the balance of probabilities, an injury was caused as a direct result of their participation in the study. These special compensation arrangements apply where an injury is caused to the participants that would not have occurred if

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they were not in the study. These arrangements do not affect your right to pursue a claim through legal action.

10.6 Finance and Funding

To date, the UK ITP Registry has received funding from:

- Barts Health Charity
- NIHR
- ITP patient support association
- Novartis (formerly GSK): unrestricted educational grants
- Amgen: unrestricted educational grants

10.7 Dissemination of Research Findings

Analyses of registry data will be carried in stages throughout the life span of the registry; results from these investigations will be presented at haematology meetings and published in peer-review journals, in our study newsletter, and, where appropriate, in *The Platelet*, the official newsletter of the ITP Support Organisation.

11 REFERENCES

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12 APPENDICES

12.1 Appendix 1 - guidance on sample collection, storage and transfer.

Sample collection, transfer and storage for the ITP Registry Sample

Before collecting any biological sample

Please check that the participant has agreed and consented to donate a sample for use in research

When to take blood and what precaution should be used during registration?

The blood sample should be taken at the time that the participant agrees to be part of the Registry. If it is not possible to take a sample on this occasion, this can be done on the next outpatient or hospital visit as arranged between the staff and the participants. If participating sites are unsure whether the samples have been sent, this can be checked by contacting the registry team.

Please follow the following steps and procedures

Please observe standard (universal) precaution when taking and handling biological samples

Using standard venipuncture techniques, take a 4-8 ml blood sample with a standard EDTA (purple top) tube.

Label sample collected with the date of sample collection and the Registry Identification Code (RIC). This should be obtained from the Participants Log for your centre. Identifying information should not be put on the sample.

How long to store the blood if sample is stored before transfer, what temperature is the sample required being stored?

If dispatching is possible within 24 hours it can be kept at room temperature.

If shipping will happen in 1 to 3 days please keep the sample on or in a medical fridge (about 5 °C)

PLEASE DO NOT FREEZE (i.e. DO NOT STORE AT 0 °C OR BELOW)

Do not consider sending blood sample on Friday or a day before a bank holiday.

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What are the minimum requirements for sample transfer and package?

General packaging and transfer requirement for biological substances is Category B

Packing for exempt patient specimens must be packaged and marked according to the biological substance, category B, UN 3373³

The sample should be packaged in the following (please find a link to the full sample packaging guide in the references section above)

Wrap the sample tube in absorbent material.

The wrapped sample tube should be placed into the plastic leak-proof packaging bag.

Tightly close the top of the plastic leak-proof packaging container.

An outer packaging of adequate strength for its capacity, mass and intended use (fibreboard, wood, or rigid plastic), and with at least one surface having minimum dimensions of 100 mm x 100 mm.

You could use Safe box™ from Royal Mail for secure package or any similar services using mailboxes for biological sample which comply with the triple packing safety requirement is needed as described above.

Sample labels are available on the Registry website www.ukitpregistry.com.

The address for sending blood samples for genetic analysis (i.e. 4 to 8 ml purple top container):

UKITP Registry
4th Floor Haematology Laboratory
Pathology & Pharmacy Building
The Royal London Hospital
80 Newark Street
London
E1 2ES

If you have any queries please contact.

Study Coordinator & Data Manager

Email: uk-itp.registryteam@nhs.net

T: 0207-377-7000 ext 61114

F: 0203-246-0230

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For Royal London Hospital (RLH) participants involved in sub study:

For RLH participants involved in the sub-study up to 50ml of blood will be taken and sent to The Registry within 24-36hrs of collection. This may include one citrate, one serum and two EDTA blood samples.

Please do not send the samples to the wrong addresses as this may render the samples becoming unusable because of the time lapse it will take to redirect the samples internally to the right person.

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a. Appendix 2- units of treatment doses

12. Treatment	13. Units of Dose	14. Course length	15. Notes
Anti-D	µg	days	
Azathioprine	mg/day	days	
Cyclophosphamide	mg/day	days	
Cyclosporine	mg/week	days	
Danazol	mg/day	days	
Dapsone	mg	days	
Dexamethasone	mg/day	days	
Eltrombopag	mg/day		
IVIg	g/day	days	
Methylprednisolone	mg/day	days	
Mycophenolate	mg/day	days	
Prednisolone	mg/ day	days	Please only enter the initial dose given. We don't need tapering doses. Course length should be total duration of therapy including tapering doses.
Rituximab	mg/m ² /week	days	
Romiplostin	µg/kg/week	days	
Vinca Alkaloids	mg/week	days	

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10.8 Appendix 3 – Recommended timing of platelet count results

* +/- 14 days

Treatment	0-1 weeks	1-2 weeks	2-3 weeks	3-4 weeks	2 months*	4 months*	6 months*	1 year*
Anti-D	daily counts*	✓	✓	✓	✓	✓	✓	✓
Azathioprine	✓	✓	✓	✓	✓	✓	✓	✓
Cyclophosphamide	✓	✓	✓	✓	✓	✓	✓	✓
Cyclosporine	✓	✓	✓	✓	✓	✓	✓	✓
Danazol	✓	✓	✓	✓	✓	✓	✓	✓
Dapsone	✓	✓	✓	✓	✓	✓	✓	✓
Dexamethasone	daily counts*	✓	✓	✓	✓	✓	✓	✓
Eltrombopag	✓	✓	✓	✓	✓	✓	✓	✓
IVIg	daily counts*	✓	✓	✓	✓	✓	✓	✓
Methylprednisolone	daily counts*	✓	✓	✓	✓	✓	✓	✓
Mycophenolate	✓	✓	✓	✓	✓	✓	✓	✓
Prednisolone	daily counts*	✓	✓	✓	✓	✓	✓	✓
Rituximab	✓	✓	✓	✓	✓	✓	✓	✓
Romiplostin	✓	✓	✓	✓	✓	✓	✓	✓
Vinca Alkaloids	✓	✓	✓	✓	✓	✓	✓	✓

*Please give as many count as are available in this time period

Please use this table to guide which platelet counts need to be entered on the database. The time frames start from the day that treatment is initiated. No specific clinic visits are required; the time which is closest to the defined period should be entered.

Annual update of information is recommended where possible, if a patient has a repeat treatment episode, the above table should be used to guide data entry