

UKITP REGISTRY STUDY PROTOCOL 2.3

UKITP STUDY PROTOCOL 2.2



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**

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REC Reference **07/H0718/57**

Sponsor reference or ReDA **005148**

IRAS Project ID **92703**

Chief Investigators **Dr Vickie McDonald**

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1 Glossary

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

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2 SIGNATURE PAGE

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Chief Investigator Agreement

The clinical study as detailed within this research protocol (UKITPR Study Protocol 2.3, dated 16th May 2018), 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.

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Chief Investigator Name: Dr Vickie McDonald

Chief Investigator Site: Barts Health NHS Trust

Signature and Date:

Sub-Investigator Name: Dr Sue Robinson

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

Signature and Date:

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Other staff members involved:

Name: Dr Drew Provan

Site: Barts Health NHS Trust

Signature and Date:

3 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.

<u>Short Title</u>	<u>UKITP registry</u>
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¹ Natural progression shall be defined as platelet count, bleeding events, and mortality over time.
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<u>Methodology</u>	<u>A UK-wide registry of patients with ITP</u>
<u>Research Sites</u>	<u>Barts Health NHS Trust and Queen Mary, University of London with other NHS Trusts as data collection centres</u>
<u>Objectives/Aims</u>	<u>To better understand the causes, treatment responses and outcomes in patients with ITP</u>
<u>Number of Participants/Patients</u>	<u>No restriction – open to all patients in the UK with ITP who fit the eligibility criteria</u>
<u>Main Inclusion Criteria</u>	<u>Adults (age >18 years) with primary ITP or pregnancy-associated ITP</u>
<u>Main Exclusion Criteria</u>	<u>Secondary ITP, patients <18years of age, patients unwilling to consent</u>
<u>Statistical Methodology and Analysis (if applicable)</u>	<u>N/A</u>
<u>Proposed Start Date</u>	<u>Commenced 2007 (REC 07/H0718/57)</u> <u>Previous Substantial Amendment (5 - 12/06/2017)</u> <u>12th June 2018</u>
<u>Proposed End Date</u>	<u>31 May 2020</u>

Study Protocol

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UKITP REGISTRY STUDY PROTOCOL 2.3

UK Adult Immune Thrombocytopenic Purpura (ITP) Registry

Purpose:

This study seeks to uncover information regarding the natural progression¹, 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 Research Ethics Committee (MREC) in 2002 under the title, "Establishment of a UK Registry for Adults with Immune Thrombocytopenic Purpura (ITP) and Investigation into the Role of Cytokine Genes." The study was ethically approved in August 2002 (MREC/02/2/58) and remained highly active until August 2005, during which time over 600 patients were enrolled.

Due to unforeseen circumstances, which resulted in a temporary switch of positions, the chief investigator was forced to slow analysis of the cohort at this time. He has since returned to The Royal London Hospital as both a consultant haematologist and senior clinical lecturer 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 GlaxoSmithKline (GSK) Inc. and The ITP Support Association.

4 Introduction

Primary Immune Thrombocytopenia (ITP) is a rare bleeding diathesis, characterised 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 is interested in collecting data that will offer better insight into understanding 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 will also include ongoing, prospective data collection regarding the management and outcome of pregnancy in 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 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.

5 Trial Study Objectives

5.1 Primary Objectives:

To collect adequate data and biological samples on primary ITP in order to investigate its epidemiology, aetiology, prognosis, treatments and outcomes throughout all stages of adult life (including pregnancy).

5.2 Secondary Objectives:

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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.

Design & Methodology:

Recruitment & Consent:

The proposed protocol entails investigation of prospective and past study participants. Adult patients presenting at haematology clinics at The Royal London Hospital or collaborating centres with a low platelet count ($< 100 \times 10^9/L$)² and no evidence of known thrombocytopenic inducing disease or treatments following a standard ITP workup will be invited to take part in the study. ~~Any patients who were diagnosed with ITP at any time, even prior to the publication of the latest international consensus in 2010, will continue to be enrolled onto the registry. At The Royal London Hospital, recruitment and informed consent will be conducted by the chief investigator and two clinical investigators.~~

~~These tasks will be directed by members of the chief investigator's team³ at all other external clinics. Consultant haematologists at these sites will be issued a study overview (UKITP Haematologist Overview 2.4) and asked to identify all eligible patients. Following a brief introduction to the investigation, consultants will ask patients for their permission to forward their name and address to the data manager.~~

~~These patients will subsequently be mailed a comprehensive, lay overview of the study (UKITP Prospective Participant Overview 3.1), which will contain means through which to contact both the chief investigator and study coordinator with any pre or post-enrolment questions or concerns. Included with this paperwork will be two informed consent agreements, concerning the study and subsequent tissue storage respectively, returnable to~~

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

² - Following the international consensus on diagnosis of ITP (Provan et al, 2010), the platelet count criterion changed from 150×10^9 to $< 100 \times 10^9$. All patients on previous diagnosis base on platelet count $< 150 \times 10^9$ will continue to be enrolled.

³ - The chief investigator's team shall be comprised of the Chief Investigator, the Lead Epidemiologist, and the Data Manager.

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the study coordinator via a pre-paid, self-addressed envelope. Originals of this paperwork will be kept on file at The Royal London Hospital.

6 Methodology

6.1 Inclusion Criteria

- 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.

6.2 Exclusion Criteria

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

7 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 proposed protocol entails 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.~~

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.

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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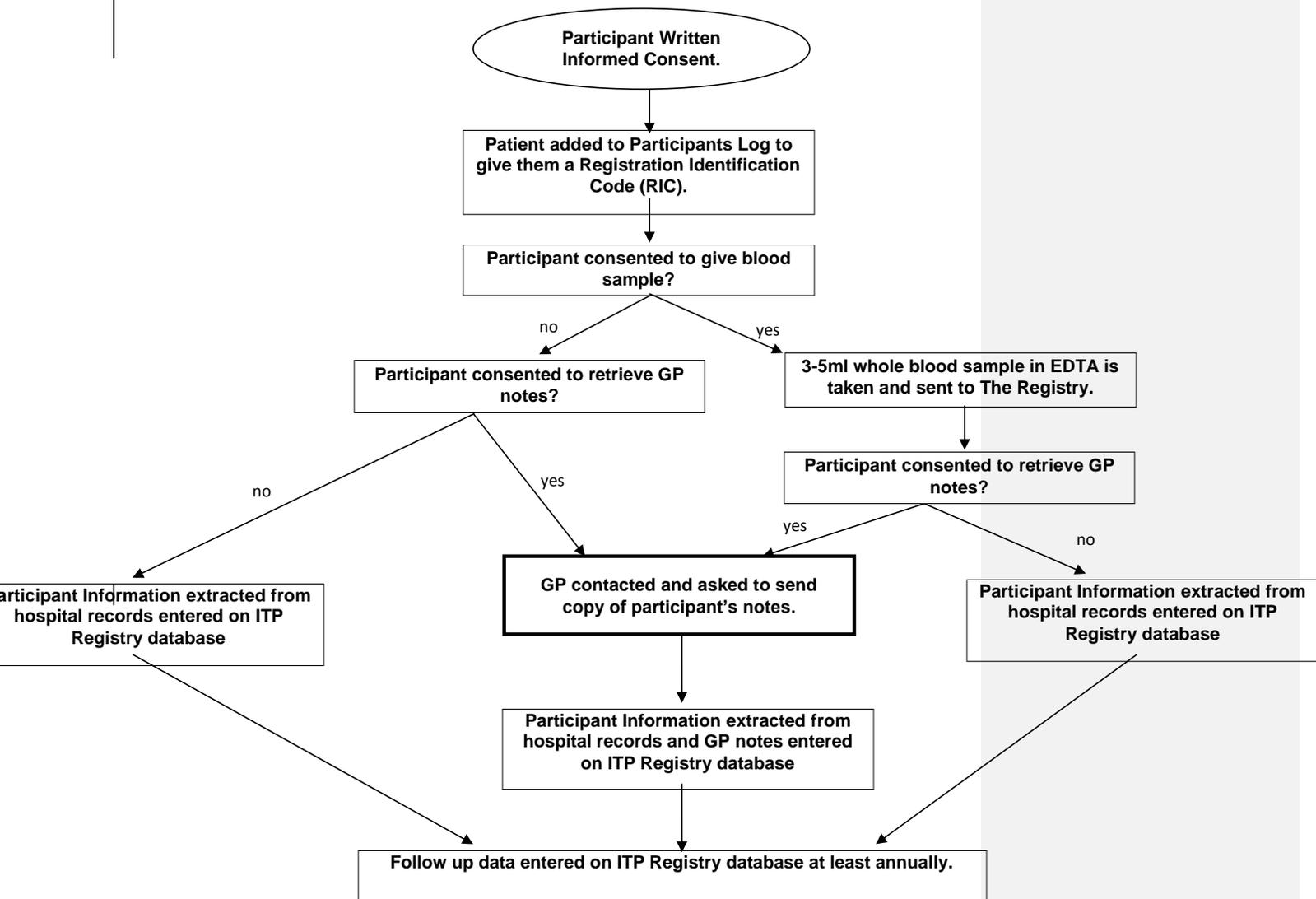
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7.1 Study Scheme Diagram



9. Blood Collection & Genetic Testing:

At the time of registration, one blood sample (15 ml, ~3 teaspoonsful) will be drawn during a routinely scheduled venepuncture (or a saliva sample [Oragene® kit]) and mailed to the study coordinator, who will be responsible for its semi-anonymisation via labelling with a uniquely allocated study number. For some patients, especially those who are seen at the Royal London Hospital, an additional 20mls of blood will be collected for T cell analysis. The Chief Investigators team will inform the patients if this is required during their visit at the hospital. All samples collected will be sent to The Molecular Haematology Laboratory at The Royal London Hospital and/or Blizzard Institute for safe storage and analysis.

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.

Blood Collection for Immune Profiling:

A subset of patients will be invited to contribute up to four blood samples of 50mls (10 teaspoons) over a six month period for detailed analysis of anti-platelet antibodies, B and T cell profiling, and B and T cell responses to autoantigens. Existing registry patients or those who have expressed an interest in participating as outlined in the section on Recruitment & Consent above, will be given the updated patient information leaflet (UKITP Prospective Participant Overview 3.1) with a verbal explanation of the substudy, by their usual physician, during the course of a routine consultation. Donations will be obtained at a subsequent routine visit, when patients have had a minimum of 24 hours to consider their involvement in the study.

The first blood of 50 mls will be used for analysis of anti-platelet antibodies. This analysis is performed in patients as part of routine service and if such an analysis has been undertaken within the previous three months it will not be repeated.

The subsequent blood samples will be used for analysis of leucocyte surface markers using flow cytometry, for B cell and T cell functional assays to determine responses to autoantigens found in ITP, autoantibody assays and analysis of gene and protein expression. During the course of the cellular assays, blood samples will be transported to GSK laboratories and other 3rd parties at GSKs discretion, for completion of analysis. All samples will be stored in accordance with the HTA guidelines and tracked using GSKs human biological samples management database. Any remaining samples will be destroyed at the end of the study.

Medical Record Extraction Procedure:

During the defined ten-year study period, standard proforma will be used to extract information from participant hospital medical records at registration and on a schedule determined by the local centres but it will be done at least once annually. Some centres may wish to collect information more frequently than yearly because the study related data are readily available soon after participants are seen by their haematology teams. Some may find it more manageable to perform data collection on a case by case basis than several at a time. Others may wish to schedule specific points in time to collect data on all their participants. The registry can assist any centres decide on the best data collection schedule that suits them. Whatever schedule a particular centre wishes to adopt will be entirely its own decision. For study participants registered at The Royal London Hospital, these extractions will be undertaken by the registry's team. The data detailed under the heading 'Field for Extraction'

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~~will be directly entered into an electronic study database and cross-verified. Should inconsistencies arise during this check, a subsequent extraction will be performed and similarly cross-verified. At all other collaborating centres, a member of the patient's clinical care team will be responsible for performing the scheduled extractions and for forwarding the abstracted data to the chief investigator's team using a secured server.~~

~~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. This may be attributed to several potential reasons:~~

~~At presentation or registration~~

~~1. Not all the information which is relevant to the study may have been sent during referral to RLH or collaborating centres, especially for participants who were diagnosed quite some time before their registration onto the study.~~

~~During follow up~~

~~1. After some time, certain patients may have been discharged to other healthcare centres for monitoring or ITP management, e.g. general practitioners.~~

~~2. Some patients may migrate to other regions within the UK and require to be followed up.~~

~~3. A minority of patients may have unfortunately passed away which require to be recorded.~~

~~To address these situations, we will search new and existing NHS services. Some of these services were introduced to improve access to data and allow follow up of patients for various clinically important reasons and to facilitate research.~~

~~At the Royal London Hospital, just like many other NHS healthcare providers, the highly secure Spine portal will come into place to allow access to patients' data under the 'Connecting for Health' scheme. Summary Care Records is the service that we will use to obtain up-to-date key health information on our participants. Only data that are required for our study will be extracted from this source. However, this service is still being updated nationally (mainly by general practice) and data may not be available for many patients yet.~~

~~We recognised that general practitioners are more likely to be up-to-date about the patients' overall conditions and care. They may also be involved in monitoring ITP patients and may also be involved in their management. We will therefore contact them to request certain information. The data that we will ask GPs to provide are the same that we will be gathering from the collaborating centres. What we require from general practitioners is described in the proforma (version 1.0) which will be accompanied by a letter (GP letter version 1.0) that outlines our research aims and the reasons behind our request.~~

~~The Data Linkage Services provided by Health and Social Care Information Centre is the NHS research resource that we will engage. This is a highly secure service which can trace patients records for certain study-related data, such as demographic status and mortality (including cause of death or whether certain patients is not in the UK) and hospital episode information (e.g. certain diagnoses or operations). Therefore, this valuable tool will aid our effort to reduce lost to follow up and obtain more up-to-date study-related data about our participants.~~

~~These resources are important to this study and will ensure that our data is as complete and up-to-date. Below is a list of the fields on which we wish to extract data from the various sources mentioned.~~

STUDY PROCEDURES

8.1 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.

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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 3-5ml of blood for genetic studies into ITP
5. Collection of data on the management of ITP during pregnancy and the outcome of a participants' pregnancy.

8.2 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.

8.3 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.

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

8.4.1 Samples for genetic analysis

At the time of 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 Platten

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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.

8.4.2 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.

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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.:

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.

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In addition to ITP patients, 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.

8.5 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 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.

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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.

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8.5.1 General Practitioner (GP) Notes

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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 at participants' registration. ITPR General Practitioner Letter template UK 1.9 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 notes will be sent straight back to the site team instead of via the Registry as it was previously.

Fields for Extraction

~~The fields that are for data collection at registration are listed below. Some of them are also for collection during follow up and are marked "FU" accordingly.~~

~~Demographic, anthropometric and healthstyle information:~~

~~3~~

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~~Patient Name and Contact Address^{+FU}
- Patient Gender
Patient Date of Birth Ethnicity
Patient Weight at Diagnosis
Patient Height
BMI at diagnosis^{+FU}
Smoking status^{+FU}
Alcohol consumption^{+FU}~~

~~Referral centre information at diagnosis and registration (if different)
Name of referrer
Specialty of referrer
Centre name and contact address
Centre phone and fax numbers~~

~~Current Hospital and Haematologist
• Name^{+FU}
• Centre Name and Contact details^{+FU}~~

~~Key information and dates:
Registration Date
NHS number
Name, specialty and address of healthcare practitioner(s) who made ITP diagnosis
Date of Diagnosis
Date of Last Clinic Visit^{+FU}~~

~~Bleeding Events^{+FU} (yes/no, severity, date)
Cutaneous Bleeds
Bleeds from the Oral Cavity Epistaxis
Uterine Bleeds
Haematuria
Gastrointestinal Bleeds
Intracranial Haemorrhage
Muscle Bleeds
Joint Bleeds
Subconjunctival Haemorrhage
Retinal Bleeds~~

~~Treatment^{+FU} (Yes/No; Date(s), Dosage(s) & Duration(s) where applicable)
Prednisolone
IVIg
Splenectomy (Laparoscopic/Open Technique) Anti-D
Methylprednisolone
Dexamethasone
Danazol
Dapsone
Azathioprine
Cyclophosphamide
Vinca-Alkaloids
Mycophenolate
Eltrombopag~~

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Romiplostim
Plasmapheresis
 Protein A-Immunoabsorption
 Interferon
 Cyclosporine
 Rituximab
Platelet Transfusion
 Red-Blood-Cell-Transfusion
 H. pylori Treatment
 Vitamin-C
Supplements-Co-therapies
Anti-lipid therapy
 Antihypertensive therapy
 Anticoagulation therapy
 Thrombolysis therapy
 Antifibrinolytic therapy
 Other

Co-Morbid Conditions^{+FU} (Yes/No, Date of diagnoses)
Cataracts
Osteoarthritis
 Type I Diabetes
 Type II Diabetes
 Hypertension
Peptic Ulcers
H. pylori Infection
 Renal Failure or Impairment
 Chronic Liver Disease
 Hypercholesterolemia
 Myocardial Infarction
 Unstable Angina
 Revascularisation procedure
 Sudden cardiac death
Ischaemic Stroke
 Transient Ischaemic Attack
 Deep Vein Thrombosis
 Pulmonary Embolism
 Splenomegaly
Thyroid Disease
 Depression/Anxiety
 Miscarriage
 Cushing's Syndrome
 Candida Infection
Pneumonia
 Other Autoimmune Disease
 Haematological Malignancy
 Solid Tumour/Malignancy
 Phototoxicity
Other

Family history^{+FU}
Cancer
 Ischemic Heart
 Disease Stroke
 ITP or other autoimmune disease
 Any other relevant family history

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Biochemical Fields (Levels at Diagnosis)

- Alanine Transaminase (ALT)
- Aspartate Transaminase (AST)
- Alkaline Phosphatase (ALP)
- Bilirubin

Haematological Fields

- Platelet Count(s) (Count & Date) ^{+FU}
- Haemoglobin ^{+FU}
- White Blood Cells (Level at Diagnosis) [Neutrophils ^{+FU}
- Red Blood Cells Count (Level at Diagnosis) Mean Platelet Volume (MPV) [Volume at Diagnosis]
- Blood Group (A, B, AB & O; Rh Positive/Negative) Marrow Aspirate (Yes/No, Conclusions)
- Trephine Biopsy (Yes/No, Conclusions) Direct Agglutination Test (DAT) (Level at Diagnosis)

- IgG
- IgM
- IgA

Anti-Nuclear Antibodies

- Coagulatory Fields (Levels at Diagnosis) Prothrombin Time (PT)
- Activated Partial Prothrombin Time (APPT)
- Lupus Anticoagulant (LA)
- Anticardiolipin Antibody (aCl)
- Reticulocyte Percentage

Diagnostic Information:

- Change of ITP Diagnosis (Yes/No) ^{+FU}
- Indium Scanning (¹¹¹In ¹²⁰min spleen/liver ratio, date) ^{+FU}
- Clinical contacts and resource utilisation (mainly at RLH and some centres ⁴)
 - Hospitalisation
 - Clinic visits

Other

- Mortality and cause of death

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8.5.2 Fields for extraction from medical and other related-records

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):

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<u>FieldsHeadings for extraction</u>
<u>Demographic, anthropometric and lifestyle information</u>
<u>Referral centre information</u>
<u>Bleeding Events</u>
<u>ITP Treatments</u>
<u>Co-therapies</u>
<u>Co-Morbid Conditions</u>
<u>Family Disease History</u>
<u>Blood counts- including biochemistry and coagulation fields</u>

Diagnostic Information
Mortality
Adverse events and related information

8.6 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.

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

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Pregnant Adult 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 in pregnancy where: ~~where a clinical decision to treat the thrombocytopenia prior to delivery of the infant has been made~~

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.

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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 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.

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Please note that this part of the Registry will be lead 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 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.

8.6.1 Fields for extraction for ITP during pregnancy

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

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Data Protection:

The collection of information from medical records at The Royal London Hospital will be performed by the chief investigator's team. For participants at all other centres, the data retrieval process will be conducted by a member of the local clinical care team. Access to hospital medical records at these sites will be extended to the chief investigator's team but will be limited to monitoring and quality assurance purposes only. To note, our current data protection safeguards which are in place also match the requirements expressed by the HSCIC for using its Data Linkage Services.

Importantly, all information collected will be kept strictly confidential. Any published data will be anonymised so that participants cannot be identified from it. Annually during the study, fully anonymised data will be shared with medical researchers at GlaxoSmithKline Research Ltd. and the Paediatric & Adult Intercontinental Registry on Chronic Idiopathic Thrombocytopenic Purpura (PARC-ITP) Study in Basel, Switzerland. These partnerships will enhance resources with which to investigate the natural progression, causes, and treatment of adult ITP while strengthening analysis of the study's findings. The information submitted to

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⁴ Centres which are able to provide this data will be invited to do so in the next registry update due at the end of 2013 and beginning of 2014.

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~~these two organisations will contain no personally identifiable material, and all planned analyses utilising it will require favourable review from a research oversight body.~~

8.7 Data Capture~~Quality and Completeness~~

Appendices 2 and 3 can be used to guide data entry as they specify units required for ITP treatment doses and timing of required platelet counts relative to treatment. Improved data quality reduces the number of data queries sent back to the centre.

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

8.8 Subject Withdrawal

Patients are free to withdraw from the Registry at any time. Their site team should contact The ITP Registry directly to have their data 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.

8.9 End of Study Definition

This extension of the study is currently due to end 31 May 2020.

8.10 Statistical Consideration

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

~~Past Study Participants:~~

~~Owing to the non-sensitive nature of the proposed revisions, The London MREC determined that it would not be necessary to re-consent past study participants. The same information will be extracted from the hospital records of past participants as from those of prospectively enrolled participants.~~

~~Participant Medical Record Extraction Analysis:~~

~~Information obtained from participants' medical records, general practices and NHS research services will be used to conduct the qualitative and quantitative analyses highlighted in Appendix A1, which includes investigating the natural progression of the disease and the effectiveness of currently implemented therapies. These analyses will be carried in stages from 2013 until the conclusion of the study in 2018; results from these investigations will be published in peer-review journals, in our 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 an electronically posted bi-monthly newsletter on our study website: www.ukitpregistry.com. They, too, will be provided with multiple means to contact the chief investigator's team regarding any questions or concerns that they may have throughout the duration of the study.~~

9 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.

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9.1 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.

9.2 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.

9.3 Data Handling and Record Keeping

Information relating to participants will be kept confidential and managed in accordance with 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 Barts 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.

9.4 Laboratories

Blood samples will be processed at Barts Health NHS Trust or Queen Mary, University of London campus. Samples will be extracted 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.

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

9.6 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](#)

9.7 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.

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IATA Packing Instruction 650 — Biological Substances, Category B
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Chief Investigator Signature:

Dr Daniel Hart - 22 February 2017

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. You can check the online database if a sample has been sent by the local centre and received by the Registry.

- 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.

- 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.

- 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

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- The sample should be packaged in the following
 - 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](tel:0207-377-7000) ext 61114

F: [0203-246-0230](tel:0203-246-0230)

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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11.2 Appendix 2- units of treatment doses

<u>Treatment</u>	<u>Units of Dose</u>	<u>Course length</u>	<u>Notes</u>
<u>Anti-D</u>	<u>ug</u>	<u>days</u>	-
<u>Azathioprine</u>	<u>mg/day</u>	<u>days</u>	-
<u>Cyclophosphamide</u>	<u>mg/day</u>	<u>days</u>	-
<u>Cyclosporine</u>	<u>mg/week</u>	<u>days</u>	-
<u>Danazol</u>	<u>mg/day</u>	<u>days</u>	-
<u>Dapsone</u>	<u>mg</u>	<u>days</u>	-
<u>Dexamethasone</u>	<u>mg/day</u>	<u>days</u>	-
<u>Eltrombopag</u>	<u>mg/day</u>	<u>days</u>	-
<u>IVlg</u>	<u>g/day</u>	<u>days</u>	-
<u>Methylprednisolone</u>	<u>mg/day</u>	<u>days</u>	-
<u>Mycophenolate</u>	<u>mg/day</u>	<u>days</u>	-
<u>Prednisolone</u>	<u>mg/ day</u>	<u>days</u>	<u>Please only enter the initial dose given. We do not need tapering doses. Course length should be total duration of therapy including tapering doses.</u>
<u>Rituximab</u>	<u>mg/m²/week</u>	<u>days</u>	-
<u>Romiplostin</u>	<u>ug/kg/week</u>	<u>days</u>	-
<u>Vinca Alkaloids</u>	<u>mg/week</u>	<u>days</u>	-

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11.3 Appendix 3 – Timing of platelet counts required

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

*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

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+/- 14 days

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