Protocol

The United Kingdom Thrombotic Thrombocytopenic Purpura Registry
(UK TTP Registry)

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Sponsor: University College of London Hospitals (UCLH)
**Full Title:** The United Kingdom Thrombotic Thrombocytopenic Purpura (TTP) Registry.

**Short Title:** UK TTP Registry

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**Author(s)** Dr Marie Scully on behalf of the UK TTP group

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**TRIAL SUMMARY**

This is a UK based registry, involving all sites treating newly presenting Thrombotic Thrombocytopenic Purpura (TTP). From this registry, important epidemiological data will be obtained. Admission and remission samples will be collected. DNA will be collected and analysed from patients wishing to participate to determine if any link exists between mutations/polymorphisms and the risk of TTP.

University College London (UCL) Haemostasis Research Unit (HRU) will collect and collate the data and help administrate for those sites participating in the registry. However, ADAMTS 13 assays will no longer be subsidised. For those sites undertaking local assays, a record of cases will be shared centrally. The UK TTP registry will be part of the UK TTP group.
LIST OF KEY PERSONNEL

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<thead>
<tr>
<th>Name</th>
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<td></td>
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<td>Department of Haematology</td>
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The UK TTP registry started in January 2009, following 3 years MRC funding, involving UK collaboration from all sites treating TTP patients. It has resulted in a cohort of data and samples from UK TTP cases. The registry promotes a collaborative approach with all UK patients and physicians involved with this life threatening disorder.
## LIST OF ABBREVIATIONS

<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADAMTS 13</td>
<td>A disintegrin and metalloprotease with thrombospondin type 1 repeats</td>
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<td>APLS</td>
<td>Antiphospholipid Syndrome</td>
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<tr>
<td>CBA</td>
<td>CBA: Collagen Binding Assay</td>
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<tr>
<td>COCP</td>
<td>Combined Oral Contraceptive Pill</td>
</tr>
<tr>
<td>CNST</td>
<td>Clinical Negligence Scheme for Trusts</td>
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<tr>
<td>CR</td>
<td>CR: complete remission</td>
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<tr>
<td>DAT</td>
<td>Direct Antiglobulin Test</td>
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<tr>
<td>DIC</td>
<td>Disseminated Intravascular Coagulation</td>
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<tr>
<td>FFP</td>
<td>Fresh Frozen Plasma</td>
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<tr>
<td>Abbreviation</td>
<td>Description</td>
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<tr>
<td>HELLP</td>
<td>Haemolysis, Elevated Liver Enzymes, Low Platelets</td>
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<td>HRU</td>
<td>Haemostasis Research Unit</td>
</tr>
<tr>
<td>HUS</td>
<td>Haemolytic Uraemic Syndrome</td>
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<tr>
<td>LDH</td>
<td>Lactate Dehydrogenase</td>
</tr>
<tr>
<td>MDSAS</td>
<td>Medical Data Solutions and Services</td>
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<tr>
<td>MRS</td>
<td>Microsoft Reporting Service</td>
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<tr>
<td>PET</td>
<td>Pre-eclampsia</td>
</tr>
<tr>
<td>PEX</td>
<td>Plasma Exchange</td>
</tr>
<tr>
<td>SE England</td>
<td>South East England</td>
</tr>
<tr>
<td>SNP</td>
<td>Single Nucleotide Polymorphism</td>
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<tr>
<td>TMA</td>
<td>Thrombotic Microangiopathy</td>
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<tr>
<td>TTP</td>
<td>Thrombotic Thrombocytopenic Purpura</td>
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1. **SUMMARY**

1.1 **Objectives**

The *primary objectives* of the study are:

Determination of the incidence, distribution of cases and epidemiology of TTP, including mortality and treatment regimes, in the UK. This incorporates congenital, acquired and secondary causes.

The *secondary objectives* of the study are:

- To determine which ADAMTS 13 assays are relevant to the clinical syndrome,
- To establish a DNA bank to determine the clinical associations of polymorphisms and mutations of the ADAMTS 13 gene,
- To generate a cohort of TTP patients and samples that may be used in future clinical research studies.

1.2 **Patient Population**

Patients presenting with an acute episode of Thrombotic Thrombocytopenic Purpura (TTP) will be asked to consent for the registry once in remission. However, for those sites undertaking ADAMTS 13 analysis, consent for admission and remission samples for TTP cases will be requested. A screening log of all cases analysed will be kept by sites and forwarded at 3 monthly intervals. This will help identify other non TTP causes for ADAMTS 13 analysis. For those sites who continue to send samples for analysis at UCL/UCLH, consent for data and remission samples remains necessary. The patients may have had a previous episode of TTP or be new cases. There is no age limit to eligibility of patients. Patients must have microangiopathic haemolytic anaemia and thrombocytopenia, normal clotting screen and raised Lactate Dehydrogenase (one and a half times the normal upper limit). Determination of precipitating causes should be undertaken, such as HIV infection, pregnancy, drugs or pancreatitis. Known or suspected malignancy or post bone marrow transplant thrombotic microangiopathies (TMA) will not be included. Specific inclusion and exclusion are detailed in section 4.1 and 4.2.
1.3 **Number of Patients**

The number of patients to be included is not limited. Ideally all patients presenting in England, Scotland, Wales and Northern Ireland, with an acute/new episode of TTP should be included. An estimate of 100 cases per year has been made in the UK based on cases per year presenting to the SE England region.

1.4 **Study design and methodology**

This is a registry requiring the collection of baseline and follow up clinical and routine laboratory data on patients presenting with acute TTP and related TMAs. A citrate sample will be taken from all patients for analysis on admission, pre treatment, and in remission, for determination of ADAMTS 13 levels as part of standard care. When patients have recovered from their TTP episode and are in remission they will be asked if they would like to participate in the UK TTP Registry. Once the patient has read the relevant patient information sheet (PIS) and has had time to ask any questions they will be asked to sign the appropriate study consent form. Inclusion in the study requires the provision of an extra blood sample (EDTA) for the extraction and analysis of DNA. As part of this study the patient also consents to the storage of their DNA and serum samples at the Haemostasis Research Unit of University College London. The serum sample is taken with other routine samples at remission as part of the patient’s standard care. Consent for ADAMTS 13 analysis is not required as this is part of patients’ normal diagnostic laboratory analysis.

Occasionally it is possible to extract DNA from recent routine blood samples that were taken from a living patient who subsequently died as a result of their TTP episode. Such routine samples are often stored in hospital laboratories as part of standard practice. If the patient’s next of kin consents for the UK TTP Registry on the patient’s behalf following death, and consents for these samples to be used for DNA extraction, this will be done if the right type of sample has been placed in hospital storage and if the sample is still viable for this purpose.
In England, Wales and Northern Ireland children between the ages of 6 and 16 years will be asked to assent for the UK TTP Registry after consent has been obtained from a parent or legal guardian. Age appropriate patient information sheets are to be given to the child prior to obtaining assent, and the parent or legal guardian may help the child to complete their assent form if necessary. In Scotland the method detailed above is to be used when the child is under 11 years of age, however children aged 11 years or more may consent for themselves after they have been provided with the PIS for 11-16 year olds.

1.5 Data to be collected

The relevant data to be collected include:

- Sex
- Date of presentation and discharge
- age of onset
- previous episodes
- presenting symptoms
- precipitating factors
- routine haematology and chemistry laboratory data at presentation, during admission and at follow up
- treatment required including number of PEX
- type of apheresis
- complications during admission
- follow up information (remission/relapse)

(See Admission Form/Case Report Form (CRF), Version 3.0, 3rd August 2010 and Version 4.0 July 2013)

The trial will be conducted in compliance with the approved protocol, International Conference on Harmonisation (ICH) guidance for Good Clinical Practice and any applicable regulatory requirement(s). R&D approval from NHS Trusts will be sought prior to study set up and patient recruitment at sites.

2. BACKGROUND INFORMATION

TTP is an acute life threatening disorder, associated with multi-organ microvascular thrombosis, typically affecting females, presenting in the 3rd/4th decade, with a mortality of 15-20% despite treatment with PEX. The majority of cases have autoimmune mediated disease, but congenital or secondary TTP cases are well recognised. Plasma Exchange (PEX) remains the primary treatment, but other therapies are required depending on disease phenotype/response to standard
therapy. The cohort would encompass national TTP admissions, subtypes at clinical presentation, and relate the clinical information to ADAMTS 13 activity/antibody titres/mutations or polymorphisms in the ADAMTS 13 gene, natural history and regional mortality.

The enzyme reduced in congenital and chronic relapsing TTP was identified as a protease required for the cleavage and normal maturation of von Willebrand Factor (VWF) known as ADAMTS 13. Despite TTP being a clinical diagnosis, a severe deficiency (<5%) of ADAMTS 13 appears specific for congenital and acquired idiopathic TTP. Acquired idiopathic TTP is often not associated with a specific underlying precipitating factor and antibodies to ADAMTS 13 can be detected. In up to 90% of cases, these are IgG (although IgM) and more recently IgA antibodies have also been described. Other secondary causes of TTP such as HIV infection, drugs or pregnancy) often have variable ADAMTS 13 activity and antibody levels. Congenital TTP is confirmed by mutational analysis of the ADAMTS 13 gene; gene defects may be homozygous or compound heterozygous.

The South East England Registry

The TTP cohort in the South East (SE) of England incorporating seven teaching hospitals has recently been published. This did not include all cases in this area, just those referred to centres with an apheresis service. In other parts of the UK the presentation rates, treatment regimes and mortality remains unknown.

It was a non-funded pilot observational study over 3 ½ years, involving 178 patients, but greater than 220 episodes. It is estimated the annual incidence is 6/million of the population. Fifty patients per year presented with acute TTP, but the overall number of episodes were greater, especially before the use of Rituximab. This monoclonal anti-CD 20 therapy in patients with autoimmune based TTP has resulted in a reduction in relapse rates, so the number of episodes in the latter 2 years were fewer than in the initial part of the registry.

From the data, the male to female ratio was 1:3, with age at presentation ranging from birth to 81 years (median age of 39 years for females and 46 years for males). A quarter of all cases were Afro-Caribbean. There was a trend, but this did not reach statistical significance, of increased treatment (i.e. number of PEX) and longer to achieve remission in this group. This needs to be confirmed on a larger scale. An increased autoimmune risk/severity of disease has been suggested in other disease such as lupus, in Afro-Caribbean populations. Larger numbers of patients are needed to determine if ethnicity has an affect on severity/response to treatment in TTP. The length of admission for treatment and the amount of treatment with PEX and other adjuvant therapies will help to identify characteristics between subgroups.

The majority of cases (approximately 80%) had antibody mediated disease, predominantly IgG antibodies to ADAMTS 13. Secondary TTP, where a defined precipitant could be determined, made up 15% of all the cases and congenital TTP accounted for 5% of the total cases. We need further information to differentiate those with severe refractory disease unresponsive to urgent treatments from those who respond to PEX alone. The role of IgG antibody titres within this group and the involvement of other antibody subgroups (such as IgG1-4) or IgA) needs further
investigation. The ADAMTS 13 antibody and activity levels are varied within the secondary TTP group. HIV associated TTP needs to be diagnosed soon after admission. Within the SE Registry, this cohort is primarily heterosexual females, responding to PEX in conjunction with highly active antiretroviral therapy (HAART). The reduction in viral load with plasma therapy results in sustained remissions.

Pregnancy associated TTP from the SE Registry, appears to be either antibody mediated or a trigger for adult onset congenital TTP. Identification of further subgroups as precipitants has been as a result of the registry and a central UK laboratory for ADAMTS 13 assays, for example, pancreatitis and paediatric associated antibody mediated TTP. In the latter group, before assay diagnosis, it would have been assumed, from the childrens’ age, they had congenital TTP.

In non-congenital TTP cases, analysis of the ADAMTS 13 gene for specific mutations and/or the presence of Single Nucleotide Polymorphisms (SNPs) would be undertaken on all samples. Local preliminary work confirms a heterozygote missense mutation (affecting exon 24) and one or more SNPs, despite having IgG antibodies to ADAMTS 13 . Evolving evidence suggests certain SNPs may influence the secretion of mutant ADAMTS 13 proteins into plasma, affecting the phenotype of the patient. Even within congenital TTP, the phenotypic presentation is varied from recurrent thrombocytopenic and microangiopathic anaemia every 2-4 weeks or only with significant exogenous insult, such as infection. A national DNA bank for all presenting TTP cases will enable a review of ADAMTS 13 genetics and differentiate between congenital and acquired cases, but may also subsequently help explain why certain individuals/subgroups have a predilection for TTP.

A baseline citrate sample, pre-treatment, is required for all patients to determine ADAMTS 13 activity and antibody levels. Patients with congenital or acquired idiopathic TTP would be expected to have ADAMTS 13 activity levels <10%. Acquired cases would also have positive antibodies, generally IgG to ADAMTS 13. Secondary cases may have a more variable range of ADAMTS 13 activity or antibody level. Further information and characterisation of these patients is required. Even within subgroups, differences in the presence of antibody may be variable.

3. STUDY DESIGN

This study is a registry of TTP admissions in the UK. Therefore, physicians will treat as current local/national protocols. The aim is to collect relevant information about patients’ baseline and TTP characteristics and review specialised assays in conjunction with their clinical presentation.
4. STUDY GROUPS

Any centre treating TTP within the UK can be included once R&D approval from the relevant NHS Trust has been obtained. Administrative help from HRU UCL will be available. Designated consultant(s)/associated lead for each site must be named. HRU, UCL will continue to handle samples from non-TTP patients in the standard manner.

4.1 Inclusion Criteria:

- Patients with a clinical diagnosis of acute TTP, defined by thrombocytopenia, MAHA which may be associated with clinical evidence of organ compromise.

- No age restriction

- Consent for addition to the Registry and collection/storage of admission information once in remission.

- Consent to collect, analyse and store EDTA sample once in remission.

- Consent to store samples once in remission (sample taken as part of standard care).

- For sites undertaking ADAMTS 13 analysis, consent to send admission and remission samples for analysis relating to TTP

4.2 Exclusion Criteria:

- Patients with cancer or transplant associated MAHA will not be included.

- Patients not wishing to be involved with the registry

4.3 Samples for collection

On Admission/Pre-treatment:
- A 5ml double spun citrate sample (platelet free plasma separated) taken on admission and/or pre-treatment. (Part of Standard Care).

In Remission/Approximately 3 months post admission:

- A 5ml double spun remission citrate sample (platelet free plasma separated) following discharge from the acute episode. (Part of Standard Care)
- A 5ml EDTA whole blood sample for DNA extraction. (Informed Consent from patient required).
- A 5ml serum sample. (Sample taken as part of Standard Care; Informed Consent required for storage and use of sample for current and future analysis of parameters related to TTP; Current tests include, IgG subtyping and Rituximab levels.)

All samples related to the trial will be kept in a designated freezer at the Haemostasis Research Unit, UCL. EDTA samples will be destroyed following DNA extraction, and only the DNA will be stored. The analysis of ADAMTS 13 is standard practice for confirmation of diagnosis. As new assay techniques are developed to improve diagnosis, prognosis or an understanding of the pathogenesis, stored frozen serum samples from registry patients may be used for their evaluation.

DNA analysis will be carried out on the whole patient cohort, or sub-groups, in order to ascertain if any of the genes identified have any relevance to the risk of presenting with TTP, the potential responses to treatment or the risk of relapse. If, from the ADAMTS 13 assays there is a suggestion that a patient may have had congenital TTP, which is confirmed when the DNA is analysed, the patient will be informed by their local haematology doctor (this procedure is considered to be part of standard care). If relevant, the patient’s family members will also have the opportunity to have their DNA tested for Congenital TTP as part of the study and will need to sign a separate consent form for relatives of Congenital TTP Patients after being issued with the Information Sheet for Relatives of Congenital TTP Patients.

Samples will be analysed for all sites that have obtained appropriate R&D approval from their NHS Trust. Assistance with the regulatory documentation will be available for all sites. UCL will not compensate the charge of sample transportation to the Haemostasis Research Unit. Individual patients and sites will NOT receive payment for additions to the Registry.
5. DATA COLLECTION

Data from all relevant sites will be derived from clinical notes and local laboratory computer based systems and entered onto the admission form/case report form. A copy of the completed admission form/case report form and a copy of the consent form (with assent form if relevant) will be posted or faxed to HRU UCL, while the originals are to be filed securely on site so that only designated staff have access. The fax machine and mail trays at HRU are only accessible to HRU staff with swipe card access; the HRU is additionally locked when no staff are present.

Data will be added to a designated password protected database once patients are consented at remission. This database is stored on a dedicated desk top computer at HRU and is backed up to an external hard drive and kept in a secure room (the hard drive will be kept in a locked cupboard when unattended).

The data for the project will be available via an online electronic register. Patients consented for the study will be identified on the online electronic register by a unique study number, initials, NHS number and date of birth. Microsoft Reporting Services (MRS) will be used to deliver reports for management of the register locally. This will also incorporate an option to download registry data into a Microsoft Excel or Adobe Acrobat format for local data analysis. The register will run on the internal NHS network using an encrypted site (HTTPS). This provides confidence to registry users that data is held and managed entirely within the NHS using approved NHS security and encryption standards.

Each participating site will access the system using a web browser (NHS standard – Microsoft Internet Explorer) with an allocated user name and password (issued to the Principal Investigator). Participating centres will have access to their own patient data and only key staff within UCL will have access to the whole database and information relating to the registry. To ease the burden of local administration there will be an automated mechanism for managing the re-issue of user accounts should these be forgotten. This will include the identification and enrolment of participating sites. IT support issues will be dealt with by MDSAS via an annual support contract.

The trial coordinator will visit all the relevant sites at least once a year to complete any data collection and provide relevant administrative support to the site. If a laptop is used for monitoring purposes it will be double password protected and patients will
be identified by their study number. All investigator(s)/institution(s) will permit trial-related monitoring, audit, Research Ethics Committee (REC) review, and regulatory inspection(s) by providing direct access to source data/documents. Data will be evaluated for compliance with the approved protocol and accuracy in relation to source documents, such as hospital records.

At least yearly review of the data will be undertaken. All paper records will be filed in locked cupboard within HRU, UCL. All paper records will be kept for 15 years within UCL/UCLH. Data handling will be in accordance with the International Conference for Harmonisation (ICH), Good Clinical Practice (GCP) guidelines, Data Protection Act (1998) and Caldicott Principles.

6. ETHICAL CONSIDERATION

All sites involved with the registry require R&D Approval from their NHS Trust. All patients require consent for transfer of data and DNA analysis.

For patients that die as a result of their acute TTP episode, consent from next of kin is to be obtained before the patient's details and hospital admission information can be submitted for the UK TTP Registry. Furthermore, consent from the patient’s next of kin is required before DNA can be extracted from any suitable routine inpatient blood samples that have been retained by the hospital as part of standard practice.

In England, Wales and Northern Ireland children between the ages of 6 and 16 will be asked to assent for the UK TTP Registry after consent has been obtained from their parent or legal guardian. Age appropriate patient information sheets are to be given to the child prior to obtaining assent, and the parent or legal guardian may help the child to complete their assent form if necessary. In Scotland the method detailed above is to be used when the child is under 11 years of age, however children aged 11 years or more may consent for themselves after they have been provided with the PIS for 11-16 year olds.

In patients where English is not their primary language, appropriate translators should be arranged so informed consent can be guaranteed.
Patients can withdraw from the Registry at any time. Any stored samples will be destroyed and information removed from the database.

7. FINANCE AND INSURANCE

The registry was supported by a 3 year grant from the MRC, which covered its development. Currently there is no grant funding for ADAMTS 13 assays. Locally funded administrative support for the registry to be conducted throughout the UK can help external sites as necessary

NHS Indemnity does not offer no-fault compensation i.e. for non-negligent harm, and NHS bodies are unable to agree in advance to pay compensation for non-negligent harm. They are able to consider an ex-gratia payment in the case of a claim.

Where studies are carried out in a hospital, the hospital continues to have a duty of care to a patient being treated within that hospital, whether or not that patient is participating in a clinical trial. The Sponsor does not accept liability for negligence on the part of employees of hospitals. This applies whether the hospital is an NHS Trust or not, and the Sponsor cannot be held liable for any breach in the hospital’s duty of care. Where the subject feels they may have grounds for legal action, they will have to file a complaint through the NHS where compensation may be provided via the Clinical Negligence Scheme for Trusts (CNST) in England, Welsh Risk Pool (WRP) in Wales, the Risk Pooling scheme run by the Northern Ireland Office or through The Clinical Negligence and Other Risks Scheme (CNORIS) in Scotland.

8. DISSEMINATION OF INFORMATION

Information from the trial will be presented at local, national and international meetings. The information will also be presented at patient TTP meeting(s). The ultimate collection of information will be submitted to a peer-reviewed journal.
9. REFERENCES


