1. Background

Thrombotic thrombocytopenic purpura (TTP) is a rare, life-threatening disorder in which platelet aggregates form blood clots mechanically destroying red blood cells. Affected individuals may develop kidney failure, damage to the nervous system and other vital organs, occasionally leading to death. While plasmapheresis based treatment is associated with good outcome for the majority of patients, it is estimated that the associated mortality rate may be as high as 10 %, and survivors may have life-long neurological deficit, or renal impairment. Treatment is intensive, associated with complications, and the disease burden for patients and the community is substantial.

Haemolytic Uraemic Syndrome (HUS) is another rare disease which shares characteristics with TTP including the destruction of red blood cells, a low platelet count (thrombocytopenia) and acute kidney failure. HUS is often preceded by an episode of diarrhoea caused by a Shiga-toxin releasing bacterium. This type of HUS is most usually encountered in children and adolescents. Atypical HUS (aHUS) is primarily a result of acquired or inherited defects in the complement pathway, though clinical manifestation may require a specific trigger.

Our understanding of TTP and HUS is still incomplete, and can be difficult to distinguish. Various scientific and clinical issues remain to be clarified, including the true incidence and frequency of TTP and HUS, their natural history in different clinical settings, including pregnancy. Uncertainty remains with respect to case definitions for diagnosis, optimal laboratory assessment and treatment regimens. There is also a need to assess the utility of emerging therapeutic agents, including monoclonal antibodies such as rituximab in TTP, and Eculizumab in HUS.

The relative rarity of these diseases is a barrier to accrual of data and material to support scientific studies, and to the undertaking of randomised prospective trials. Furthermore, the existing literature concerning clinical outcomes of patients with TTP or HUS may be biased by preferential reporting and publication of only good outcomes and/or serious or unusual events. The establishment of a national registry for all Australian patients with TTP or HUS provides an important community resource to address these issues.
The Australian Red Cross Blood Service (the Blood Service) is Australia’s national blood service. It provides a central point of contact for clinicians managing patients with TTP and HUS, as the provider of plasma for the current ‘gold standard’ therapy of plasma exchange and as a source of clinical advice.

The Monash University Department of Epidemiology and Preventive Medicine (DEPM) currently maintain a number of major registries including VSTORM (the Victorian State Trauma Registry), VOTOR (the Victorian Orthopaedic Trauma Registry), and the Victorian Cardiac Surgical Register (ASCTS). In addition the Transfusion Research Unit within DEPM is responsible for The Haemostasis Registry (regarding use of rFVIIa, NovoSeven®), the Neonatal Alloimmune Thrombocytopenia (NAIT) Registry, the Aplastic Anaemia (AA) Registry, the Massive Transfusion Registry and the Venous Thromboembolism (VTE) Cohort Study.

Aims

The aims of the TTP Registry are to:

- Better define the incidence, natural history, specific clinical characteristics, and clinical outcome of patients with TTP and HUS
- Provide information on the range of therapeutic strategies employed in the treatment of TTP and HUS patients
- Explore factors influencing clinical outcomes
- Help define optimal management of patients with TTP and HUS
- Inform and inspire future hypothesis-driven research in this area.

2. Study Design

The TTP Registry is a register of patients who develop TTP or HUS in any clinical setting. Clinical data collection will be undertaken by clinicians in specialist units at participating hospitals. Data management and analysis will be undertaken by the Department of Epidemiology and Preventive Medicine (DEPM), Monash University and interpreted with the input of Transfusion Medicine Specialists at the Blood Service and specialist clinicians on the steering committee. The Registry began collecting data in July 2008.

3. Study Population

Patients are identified by the treating clinician, or the Blood Service clinicians as a result of referral for provision of blood components. Patient liaison and registration will take place in participating hospitals. Recruitment is facilitated by the requirement of all patients to receive blood component therapy from the Blood Service, and by the delivery of care being provided by a small group of specialised clinicians in a limited number of centres with apheresis facilities. Registry staff will maintain close interaction with key individuals working in relevant hospital areas to ensure notification of all patients.

Participants will not be excluded unless they choose to ‘opt-off’ the Registry. As mentioned, the exact incidence of these conditions is unknown, but is anticipated that 60-150 cases will be accrued each year across all participating hospitals.
Subject recruitment and enrolment

Most patients require specialised products from the Blood Service, and are largely managed by a small group of highly specialised clinicians. Registry staff will maintain close interaction with key individuals working in relevant hospital clinical care areas to ensure notification of all patients.

4. Study Assessments

Assessments

Inclusion on the TTP Registry does not involve any change in patient management or any procedures beyond those normally employed in the diagnosis and treatment of TTP or HUS. No additional information will be collected from participants other than that routinely collected in the diagnosis and treatment of TTP or HUS.

Potential Benefits

Participants in this project may not receive direct benefit from participation. It is possible that outcomes of the project may improve management that could benefit some of the participants as well as future patients diagnosed with TTP or HUS.

5. Data Collection

Clinical data collection will be undertaken by clinicians in specialist units at participating hospitals and some laboratory data will be collected by the Blood Service. Data management and analysis will be undertaken by the DEPM, Monash University.

Patients are identified either by the treating clinician or by the Blood Service as a result of a request for the provision of specialised products. Patient liaison and registration will take place in participating hospitals primarily through the treating clinical team. Data will be collected onto a web-based data collection form designed specifically for the study. It will record the following data for each patient:

- Patient demographics
- Background
- Clinical presentation
- Test results
- Therapy
- Clinical outcome

Registry staff will be responsible for training clinicians to use this data collection form and performing random audits on 5% of cases to ensure accurate extraction of data.
6. Data Management

Patient data will not be de-identified on entry to the Registry. All participants will be recruited independently on diagnosis of TTP or HUS. Subsequent presentations may be treated at different institutions and by different clinicians. In order to completely describe the potential course of these diseases, the ability to track an individual’s progress across these transfers is required, and this requires identified data.

It should be noted that the data to be collected remain the joint property of Monash University and the Blood Service. Data will not be used in a way that will allow individual patients to be identified. Publication will be restricted to tabulation or other presentation of aggregate data only. The data will be handled by an experienced university research unit with careful attention paid to privacy and security of the information. The DEPM and the Blood Service have impeccable track records in handling personal information.

Data collected as part of the Registry will be managed according to guidelines stipulated by the Australian Therapeutic Goods Administration and conform to Commonwealth and State privacy principles. All Registry data entry will be performed by data collectors at hospitals using a web-based interface. Hospital-level access is granted to only allow a data collector access to their own patient’s information with logins assigned by Registry IT staff via email. The web interface was developed in Microsoft ASP.NET 2.0 and hosted on an IIS Web Server by the faculty’s IT team at the Monash Clayton site. All data storage is in a Microsoft SQL™ Server 2000 database located in the DEPM server room. Access to this server room is available only to the Unit IT manager. In case of fire or loss of data, the database server is mirrored each day to a backup facility at the Monash Clayton campus. All traffic between the data collector’s browser, the web server and the database server are encrypted to 128 bits, and all passwords are encrypted in the database.

Registry information is only available to the investigators named below for the purposes of developing aggregate data reports and analysis. These reports will be provided to the Steering Committee of the Registry and to participating institutions in de-identified form.

Quality control

A number of validation measures will be incorporated into the web interface to ensure quality data entry. All mandatory fields will be required to be entered, and value and date text boxes have specified upper and lower limits. Fields dependent on the value of a parent item will be enabled and disabled accordingly and warning messages will appear for unknown or extreme values. Consistency checks will also be in place. Data entry will be verified independently by TTP Registry staff. Data will be readily available for extraction and reporting to the Project Manager.
Audit

A comprehensive audit plan will be instituted to ensure a high standard of data acquisition across multiple sites using multiple data collectors. The audit plan will have two arms:

- Case accrual audits will be undertaken by cross-reference to testing and product provision by The Blood Service to ensure that all eligible cases are included.
- Random audits of 5% of cases against source data will be undertaken to ensure accurate extraction of data. This audit will be undertaken by Registry staff.

Performance figures will be reported back to data collectors and senior clinicians at each site.

Data Access/Usage

A protocol to facilitate access to researchers will be developed. In general access to TTP Registry data will be provided to bona fide external researchers with the approval of the Registry staff and the Steering Committee and with appropriate HREC approval. Participating clinicians or hospitals are at liberty to publish their own hospital data without any reference to the TTP Registry.

7. Reporting

The Registry will develop on-line Hospital Data Reports to participating clinicians and hospitals describing essential statistics relating to case accrual and outcome. A more detailed written report will be provided on an annual basis to clinicians, participating hospitals and their Ethics Committees. Six monthly quality assurance reports will be prepared for meetings of the Steering Committee.

Communication with Participating Institutions

In addition to the on-line Hospital Data Reports, communication will be maintained with stakeholders via newsletters, emails and an Annual Investigators’ Meeting.

Publications

Publication of scientific manuscripts is a high priority for The Registry. Publications will be prepared with input where appropriate from members of the steering committee and will be submitted for comment and approval of the Steering Committee. Final content will be at the discretion of the authors. Publication sub-committees may be formed in particular areas of interest or expertise. In addition to publications, project data will be presented at Scientific Meetings and Conferences.
8. Ethics

Ethics approval for participation in the Registry has been gained from Monash University Human Research Ethics Committee (MUHREC), and The Blood Service Human Research Ethics Committee (HREC). Ethics approval will be obtained from the Human Research Ethics Committee (HREC) at each of the participating hospitals.

‘Opt-off’ Consent

Written informed consent will not be obtained from patients prior to their details being included on the TTP Registry. In this Registry data collected will not exceed data routinely required by clinicians for management of patients with TTP or HUS and will be handled by highly trained staff in a reputable epidemiological unit. The small impingement on privacy is substantially outweighed by the public interest in the improvements to patient care that may result from this project. It is the view of the project that it is impractical to seek informed, valid patient consent for participation in the project because of the difficulties that would be encountered given the nature of the condition and the type of information being collected. The integrity of the project also relies on a 100% unbiased sample being collected. We know from previous work that obtaining consent would result in a potentially biased sample with less than 70% of patients included. There are specific patient types who are less likely to consent. As a result, it has been decided that the most appropriate approach is to provide an information brochure only and allow patients to ‘opt-off’ the Registry by contacting Registry staff.

Patient Information

Patients will not be contacted specifically by the Registry. A brochure regarding the Registry will be provided to patients during consultation, containing information about the Registry and contact details for local investigators, the local ethics committee, and Registry staff. The patient will be included on the Registry and clinical information provided to the Registry unless the patient decides to ‘opt-off’. Patients will be able to ‘opt-off’ at the time of approach or at any time thereafter by notifying Registry staff.

The number of patients who choose to ‘opt-off’ is not anticipated to be large. The project operates on the basis that consent will not be sought because it would be impracticable to do so. The information brochure will indicate that the Registry will maintain the strictest control over access to the information so as to ensure maximum protection of an individual’s privacy. No information will be released about any individual unless required by law (e.g. pursuant to a court order, which is, in any event, unlikely given that more detailed and relevant information would be available at the treating hospital). Under no other circumstances would any information be made available to outside parties, or be used for other purposes by the Registry team.
9. Contacts

Investigators

Dr Shlomo Cohney: MBBS PhD

Dr Cohney is a specialist in Internal Medicine and Nephrology specialist with significant involvement in transplantation & immunology over the last 15 years transplantation. Dr Cohney established Australia’s first program to enable renal transplantation for patients who are blood group incompatible with their potential donor or possess anti-HLA antibodies against their donor. This work has also led to an interest in complement, relevant to HUS, and he has conducted research and published on clinical aspects of TTP. Dr Cohney will provide guidance to registry development including; case report forms, participation in data analysis at national level. He is the current chair of the Victorian IVIG user group, the Victorian & Tasmanian Transplant Advisory committee, and chair of the TTP Steering Committee.

Dr Erica Wood: MBBS FRACP FRCPA

Dr Wood is a Transfusion Medicine specialist with clinical and laboratory experience in specialised transfusion support for patients with TTP and HUS. Dr Wood has ongoing participation in research related to transfusion medicine and will provide supervision of Registry development including; case report forms, participation in data analysis at national level and is a member of the TTP Registry Steering Committee.

TTP Registry Coordinating Centre

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**TTP Registry Steering Committee**

The Steering Committee consists of relevant stakeholders and clinical experts, the members include:

- Dr Solomon Cohney (Chair)  Western Hospital & Monash University, VIC
- Dr Paul Cannell  Royal Perth Hospital, WA
- Dr Claire Davies  Royal Prince Alfred Hospital, NSW
- Dr Sunelle Engelbrecht  The Blood Service / Monash University, VIC
- Dr Danny Hsu  Royal Prince Alfred Hospital, NSW
- Dr Nicky Isbel  Princess Alexandra Hospital, QLD
- Dr Josh Kausman  Royal Children’s Hospital, VIC
- Dr Zoe McQuilten  The Blood Service / Monash University, VIC
- Dr Stephen Opat  Monash Medical Centre & The Alfred Hospital, VIC
- Dr Louise Phillips  Calembeena Consulting
- Dr David Roxby  Flinders Medical Centre, SA
- Dr Erica Wood  Monash University, VIC

The Steering Committee will meet at least twice per year; terms of reference of the committee include:

- Monitor the scientific progress of the project, including the data quality.
- Advise on the collection and interpretation of data.
- Assess and advise regarding performance outliers.
- Advise on scientific priorities to be addressed in data analysis and publication strategy.
- Engage in collaboration with registry staff in providing intellectual input into analysis of data and development of Registry publications where appropriate and advise on their scientific quality.
## History of changes to TTP Protocol

<table>
<thead>
<tr>
<th>Version</th>
<th>Date</th>
<th>Author</th>
<th>Summary of Revisions</th>
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<tbody>
<tr>
<td>1.0</td>
<td>21/07/09</td>
<td></td>
<td>Project Protocol created. Rename of existing document ‘Project Outline’ Replacing document ‘TTP Lay Summary’</td>
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<tr>
<td>1</td>
<td>21/7/09</td>
<td>Dr Louise Phillips, Ms Nikita Schembri</td>
<td>Original</td>
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<tr>
<td>2.0</td>
<td>30/8/10</td>
<td>Dr Rosemary McGinnes, Dr Louise Phillips</td>
<td>Sections introduced and information expanded and rearranged to improve readability. Ms Nikita Schembi removed as an investigator. Status of ethics applications removed. No change to the study design</td>
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<td>3.0</td>
<td>19/9/11</td>
<td>Dr Louise Phillips</td>
<td>Amendments re expansion of Registry to include patients with HUS. Addition of new Steering Committee members (Dr Sunelle Engelbrecht, Dr Danny Hsu and Dr David Roxby)</td>
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<td>3.1</td>
<td>31/07/12</td>
<td>Dr Simon Wilkins</td>
<td>Dr Simon Wilkins and Dr Shlomo Cohney added as investigators. Dr Louise Phillips removed as investigator. Addition of new Steering Committee members (Dr Simon Wilkins, Dr Nicky Isbel and Dr Josh Kausman). Clarification of the role of Steering Committee in publications. <strong>No change to the study design</strong></td>
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<td>4.0</td>
<td>04/01/13</td>
<td>Dr Simon Wilkins</td>
<td>Dr Simon Wilkins removed as investigator and SC member. Updates to Steering Committee member affiliations. Update of contact information. <strong>No change to the study design.</strong></td>
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