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

Sponsor’s Protocol Number: 08/0264 Version: 6.0 Date: 26th July 2018

Author(s): Professor 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. As part of NHS commissioning, we will be undertaking long term follow up, to understand the impact of acute TTP on morbidity and mortality.

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. **The UK TTP registry has been used to provide information for highly specialist commissioning via NHS England and moving forward will be required to provide data relevant to the UK TTP Group and commissioners.**

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, ADAMTS13 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.
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LIST OF CURRENT PARTICIPATING CENTRES

- Aberdeen Royal Infirmary
- Addenbrookes Hospital
- Birmingham Children’s Hospital
- Bristol Royal Infirmary
- Cardiff & Vale University Health Board
- Derriford Hospital Plymouth
- Epsom & St Helier University Hospital
- Glasgow Royal Infirmary
- Great Ormond Street Hospital
- Guy's & St Thomas NHS Trust
- Imperial College Healthcare NHS Trust
- John Radcliffe Hospital Oxford
- Leeds Teaching Hospitals NHS Trust
- Leicester Royal Infirmary
- Morriston Hospital Swansea
- Newcastle upon Tyne Hospitals NHS Trust
- Norfolk and Norwich University Hospital
- Poole Hospital NHS Trust
- Queen Alexandra Hospital Portsmouth
- Queen Elizabeth Hospital Birmingham
- Queen’s Medical Centre Nottingham
- Royal Bournemouth Hospital
- Royal Cornwall Hospital
- Royal Devon & Exeter Hospital
- Royal Edinburgh Hospital
- Royal Hallamshire Hospital, Sheffield
- University Hospitals Coventry & Warwickshire
- Royal Liverpool University Hospital
• Royal Manchester Children’s Hospital
• Royal United Hospitals Bath
• South Tees Hospital
• South Warwickshire NHS Trust
• St George’s Hospital
• UCLH
• Southampton General Hospital
<table>
<thead>
<tr>
<th>Abbreviation</th>
<th>Description</th>
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<tbody>
<tr>
<td>ADAMTS13</td>
<td>A disintegrin and metalloprotease with thrombospondin type 1 repeats</td>
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<tr>
<td>CNST</td>
<td>Clinical Negligence Scheme for Trusts</td>
</tr>
<tr>
<td>CRF</td>
<td>Case report form</td>
</tr>
<tr>
<td>DNA</td>
<td>Deoxyribonucleic acid</td>
</tr>
<tr>
<td>EDTA</td>
<td>Ethylenediaminetetraacetic acid</td>
</tr>
<tr>
<td>HIV</td>
<td>Human Immunodeficiency Virus</td>
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<tr>
<td>HSCN</td>
<td>Health and Social Care Network</td>
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<tr>
<td>HSL</td>
<td>Health Services Laboratory</td>
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<tr>
<td>HRU</td>
<td>Haemostasis Research Unit</td>
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<tr>
<td>PEX</td>
<td>Plasma Exchange</td>
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<tr>
<td>PIS</td>
<td>Patient Information Sheet</td>
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<tr>
<td>REDCAP</td>
<td>Research Electronic Data Capture</td>
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<tr>
<td>SE England</td>
<td>South East England</td>
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<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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<td>TTP</td>
<td>Thrombotic Thrombocytopenic Purpura</td>
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<td>UCL</td>
<td>University College London</td>
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<td>UCLH</td>
<td>University College London Hospital</td>
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<tr>
<td>UK TTP Group</td>
<td>Collective of TTP treating doctors in the UK</td>
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<tr>
<td>VWF</td>
<td>Von Willebrand Factor</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, immune mediated and secondary TTP causes.

The secondary objectives of the study are:

- To determine which ADAMTS13/VWF assays are relevant to the clinical syndrome,
- To establish a DNA bank to determine the clinical associations of polymorphisms and mutations of the ADAMTS13 gene.
- To generate a cohort of TTP patients and samples that may be used in future clinical research studies.
- To follow the long term impact of TTP and the effect on morbidity and mortality
- Specifically study patient subgroups identified from the registry to date eg pregnancy, elective therapy, congenital TTP

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 ADAMTS13 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 ADAMTS13 analysis. Centralisation provides an opportunity for review of current ADAMTS13/VWF assays, while continuing to contribute to a sample bank for this rare condition. For those sites that continue to send samples for analysis to UCLH/HSL, consent for data and remission samples remains necessary. Site who are sending samples for analysis to other UK centres, consent from the referring /treating clinicians will be required. The patients may have had a previous episode of TTP or be new cases, having excluded other causes for the presentation and confirmation of TTP via ADAMTS13 analysis. There is no age limit to eligibility of patients. 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 specifically included. Inclusion and exclusion are detailed in section 4.1 and 4.2.

A change to the registry will include yearly follow up proformas to determine any impact on morbidity from the acute TTP episode and sustained remission during this period. Specific consents have been created for cases who have elective therapy to prevent a TTP relapse, pregnancy in a patient with a previous diagnosis of TTP and treatment follow up for congenital TTP cases.

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 acute TTP 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

A citrate sample will be taken from all patients for ADAMTS13 analysis on admission, pre treatment, and in remission, for determination of ADAMTS13 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, University College London. The serum sample is taken with other routine samples at remission as part of the patient’s standard care. Consent for ADAMTS13 analysis is not required as this is part of patients’ normal diagnostic laboratory analysis. However, the patients will confirm samples can be kept after analysis for future laboratory investigations.

In yearly follow up forms laboratory data including ADAMTS13 assay levels will be captured, gathered from the regional centres undertaking analysis. A yearly follow up form has also be generated for congenital TTP cases. In both
groups, a clinic based neurocognitive assessment and patient health questionnaire (PHQ-9) will be performed. Specific data from patients throughout pregnancy and the post partum period and receiving elective therapy, such as anti CD 20 treatment, to prevent TTP relapse will be collected.

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 Laboratory requirements for samples

One citrated blood sample should be taken from prior to the first PEX on admission. This can either be sent immediately at ambient temperature to arrive within 24 hours of collection or frozen and sent at a later date. If frozen, two aliquots of >0.5ml volume should be collected of double spun citrated plasma and sent on dry ice in a suitably vented container.

Serum samples can either be sent at ambient temperature with the citrate sample or frozen on dry ice after being single spun, serum separated and clearly marked as serum.

EDTA whole blood samples can be sent by post at ambient temperature.

All samples should have the patients name, date of birth, hospital or NHS number and date of collection. Samples should be sent to Dr Chiara Vendramin or Mrs Ingrid Obu at the UCL Haemostasis Research Unit.
Should ADAMTS13 activity analysis be required, please contact Mr Deepak Singh, using the referral form in the appendices.

1.6 Data to be collected

The relevant data to be collected include:

- Sex
- Date of presentation and discharge
- Previous episodes
- Precipitating factors and presenting symptoms
- Routine laboratory data at presentation and follow up
- Treatment required and duration
- Complications experienced

(See Acute Event CRF v4.0 July 2018, Elective Anti-CD20 CRF v1.0 July 2018, TTP Pregnancy CRF v1.0 July 2018, Congenital TTP CRF v1.0 July 2018, Follow Up CRF v1.0 July 2018 and Congenital Follow Up CRF v.10 July 2018)

The Registry 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. +GDPR

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 ADAMTS13 activity/antibody titres/mutations or polymorphisms in the ADAMTS13 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 ADAMTS13. Despite TTP being a clinical diagnosis, a severe
deficiency (<5%) of ADAMTS13 appears specific for congenital and acquired idiopathic TTP. Acquired idiopathic TTP is often not associated with a specific underlying precipitating factor and antibodies to ADAMTS13 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 ADAMTS13 activity and antibody levels. Congenital TTP is confirmed by mutational analysis of the ADAMTS13 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 ADAMTS13. 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 ADAMTS13 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 ADAMTS13 assays, for example, pancreatitis and paediatric associated antibody mediated TTP. In the latter group, before assay diagnosis, it would have been assumed, from the children’s age, they had congenital TTP.

In non-congenital TTP cases, analysis of the ADAMTS13 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 ADAMTS13. Evolving evidence suggests certain SNPs may influence the secretion of mutant ADAMTS13 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 ADAMTS13 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 ADAMTS13 activity and antibody levels. Patients with congenital or acquired idiopathic TTP would be expected to have ADAMTS13 activity levels <10%. Acquired cases would also have positive antibodies, generally IgG to ADAMTS13. Secondary cases may have a more variable range of ADAMTS13 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.

Since the initiation of the UK TTP registry, and specifically from the registry, we have identified important discoveries on pathogenesis and treatment for TTP patients. Specifically:

1. Patients are formally treated with elective therapy, typically anti CD20 treatment, which prevents TTP relapse. This is identified through monitoring of ADAMTS13 levels. A new PIS and consent will capture information relating to this treatment.

2. The number of cases of congenital TTP have significantly increased since the start of the registry. Patients often require long term prophylactic ADAMTS13 replacement therapy that needs to be captured re amount of treatment, type of treatment, blood counts and end organ damage, which must be captured at least on a yearly basis.

3. Patients who undergo pregnancy require more intense monitoring and treatment. A dedicated consent to cover this period of data collection has been generated.

4. TTP is going through a highly specialised commissioned process. As part of these requirements and from the UK TTP Group, yearly capture of laboratory and clinical parameters to identify long term impact of acute TTP on morbidity (or mortality) will be added to the initial PIS and consent and will be documented by sites.
3. STUDY DESIGN

This study is a registry of TTP admissions in the UK. Therefore, physicians will treat as per 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.

Once included into the registry, there will be yearly follow up for patients which will be submitted to the registry team.

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. ADAMTS13 analysis will continue from non-TTP patients in the UCLH/HSL specialist haemostasis department.

4.1 Inclusion Criteria:

- Patients with a clinical diagnosis of TTP, defined by thrombocytopenia, MAHA which may be associated with clinical evidence of organ compromise. Confirmed by severely reduced ADAMTS13 levels and/or a positive antibody screen.

- 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 ADAMTS13 analysis, consent to send admission and remission samples for analysis relating to TTP.

- Follow up laboratory and clinical data at least yearly to identify any changes.
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 ADAMTS13 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 ADAMTS13 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 emailed to uclh.ttp@nhs.net, while the originals are to be filed securely on site so that only designated staff have access. Data stored in 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. The database is a standalone REDCap instance, a mature, secure web application for managing online databases. The server is hosted on the AIMES Health Cloud in Liverpool, specifically developed for use by NHS trusts to manage sensitive data and NHS N3/HSCN Secure Network compliant. Patients consented for the study will be identified on the REDCap database by a unique study number, initials, NHS number and date of birth. REDCap 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 NHS N3/HSCN network. This provides confidence to registry users that data is held and managed entirely within the NHS using approved NHS security and encryption standards.

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.
UCL is the sponsor for this study based in the United Kingdom. We will be using information from patients and their medical records in order to undertake this study and will act as the data controller for this study. This means that we are responsible for looking after patient information and using it properly.

Patients rights to access, change or move information are limited, as we need to manage information in specific ways in order for the research to be reliable and accurate. If patients withdraw from the study, we will keep the information that we have already obtained. To safeguard patient’s rights, we will use the minimum personally identifiable information possible.

6. ETHICAL CONSIDERATIONS

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 ADAMTS13 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


11 Appendix 2: The TYM test and PHQ-9
TEST YOUR MEMORY
The TYM Test

PLEASE WRITE YOUR FULL NAME……………………………………………………………
TODAY IS .....................DAY
TODAY'S DATE IS THE : ........ OF ...........(MONTH) 20.....
HOW OLD ARE YOU? .................YEARS
ON WHAT DATE WERE YOU BORN? ........../ ..........(MONTH) 19.....

PLEASE COPY THE FOLLOWING SENTENCE:
GOOD CITIZENS ALWAYS WEAR STOUT SHOES
........................................................................................................................................

PLEASE READ THE SENTENCE AGAIN AND TRY TO REMEMBER IT

WHO IS THE PRIME MINISTER? ................. .................
IN WHAT YEAR DID THE 1ST WORLD WAR START?.........................

SUMS
20 – 4 = ............
16 + 17 = ............
8 x 6 = ............
4 + 15 - 17 = ............

PLEASE LIST FOUR CREATURES BEGINNING WITH “S”
e.g. Shark
1 S......................
2 S......................
3 S......................
4 S......................

WHY IS A CARROT LIKE A POTATO?........................................................................
WHY IS A LION LIKE A WOLF? ...............................................................................

REMEMBER: GOOD CITIZENS ALWAYS WEAR STOUT SHOES

Version 6.0, 26th July 2018
PLEASE NAME THESE ITEMS

1..........................
2..........................
3..........................
4..........................
5..........................

PLEASE JOIN THE CIRCLES TOGETHER TO FORM A LETTER (IGNORE THE SQUARES)

PLEASE DRAW IN A CLOCK FACE, PUT IN THE NUMBERS 1 – 12 AND PLACE THE HANDS AT 9.20

WITHOUT TURNING BACK THE PAGE, PLEASE WRITE DOWN THE SENTENCE YOU COPIED EARLIER:

-------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------------

FOR THE TYM TESTER
HELP GIVEN:  NONE/TRIVIAL/MINOR/MODERATE/MAJOR
TICK BOX IF ANSWERS WRITTEN FOR PATIENT  □
www.tymtest.com © jnbrown 2008

V 1.0 26th July 2018  UK TTP Registry

/50
# Patient Health Questionnaire-9 (PHQ-9)

Over the last 2 weeks, how often have you been bothered by any of the following problems? (Use "✓" to indicate your answer)

<table>
<thead>
<tr>
<th></th>
<th>Not at all</th>
<th>Several days</th>
<th>More than half the days</th>
<th>Nearly every day</th>
</tr>
</thead>
<tbody>
<tr>
<td>1. Little interest or pleasure in doing things</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>2. Feeling down, depressed, or hopeless</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>3. Trouble falling or staying asleep, or sleeping too much</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>4. Feeling tired or having little energy</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>5. Poor appetite or overeating</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>6. Feeling bad about yourself — or that you are a failure or have let yourself or your family down</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>7. Trouble concentrating on things, such as reading the newspaper or watching television</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>8. Moving or speaking so slowly that other people could have noticed? Or the opposite — being so fidgety or restless that you have been moving around a lot more than usual</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
<tr>
<td>9. Thoughts that you would be better off dead or of hurting yourself in some way</td>
<td>0</td>
<td>1</td>
<td>2</td>
<td>3</td>
</tr>
</tbody>
</table>

For office coding: __ + ___ + ___ + ___

*Total Score: __

If you checked off any problems, how difficult have these problems made it for you to do your work, take care of things at home, or get along with other people?

<table>
<thead>
<tr>
<th>Not difficult at all</th>
<th>Somewhat difficult</th>
<th>Very difficult</th>
<th>Extremely difficult</th>
</tr>
</thead>
</table>

V1.0 26th July 2018

UK TTP Registry

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