

Dear Colleagues,

with the first major Registry publication in *Haematologica* 2019 we have reached an eagerly awaited milestone after many years of hard work. I would like to thank all of you for your contributions to the Registry over all those years, that helped shape the clinical picture of ultra-rare hereditary TTP and to identify unmet needs to improve patient care.

By the end of 2019, we had participating sites in 18 different countries having a part in this project.

All contributions are important, but special thanks go to Prof. Masanori Matsumoto and Dr. Kazuya Sakai from Nara (Japan) who have set out to obtain new IRB/EC approval for over 50 different sites and reconsent all of their nearly 70 patients, which became necessary due to a new research law in Japan.

Best wishes,

  
Johanna Kremer Hovinga

**HIGHLIGHTS OF 2019**

- FIRST MAJOR PUBLICATION IN PRINT (VAN DORLAND ET AL.)
- AVAILABILITY OF THE NEW DATABASE
- ENROLLMENT OF 20 CONFIRMED PATIENTS
- OPENING OF NEW STUDY SITES
- PUBLICATIONS, AWARDS AND PRESENTATIONS

**OUTLOOK 2020**

- NEXT MANUSCRIPTS BASED ON PROSPECTIVE DATA
- MIGRATION OF DATA TO THE NEW DATABASE
- ANNUAL FOLLOW-UP
- FINALIZE NEW COLLABORATION AGREEMENTS

**PATIENTS SCREENING AND ENROLLMENT**

In 2019, the Registry was in contact with physicians and nurses, patients and their family members of 67 new potential hTTP patients and negotiated a collaboration with the French TMA Registry. Of these, so far 20 confirmed patients and one family member have been enrolled and their data entered in the new database.

For an additional 28 confirmed patients from Bangladesh, Canada, Egypt, Germany, and a new site in Switzerland local/national IRB/EC approval is pending, and for two new sites in the Czech Republic and Israel the collaboration agreements awaiting legal clearance. Molecular analysis for confirmation of hereditary TTP is underway for patients from India, the USA and Germany.

After solving IRB issues for the US sites with the help of the University of Oklahoma, and by providing additional resources for enrollment as well as follow-up, 16 potential patients from the US were screened, and four newly enrolled.

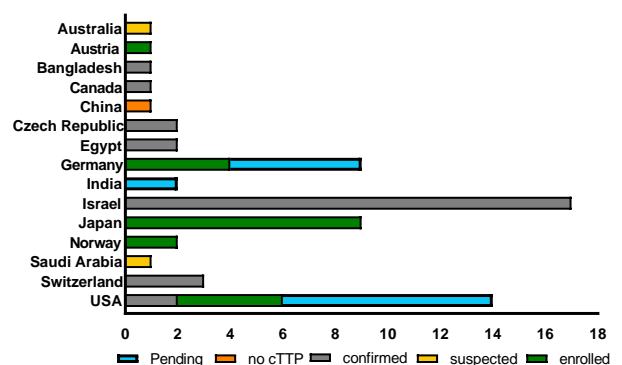


Figure 1: Screening of potential patients for enrollment by country in 2019

## NEW DATABASE

With ever increasing patient numbers and particularly prospective follow-up data of enrolled patients, problems with data linking in our electronic database became more urgent. Originally, each visit had been constructed as independent data set, e.g. different visits during one pregnancy resulted in data extracts in the same number of pregnancies as visits, requiring

Participant category	Number of participants in Old Database	Number of participants in New Database
Confirmed patients	139	20
Suspected patients	12	0
Family members	42	1
Patients misdiagnosed	16	0
Participants not meeting inclusion criteria	1	0
TOTAL	210	21

Figure 1: Participants in the Registry stand 31.12.2019

manual corrections. Initially, we tried to address inconsistencies with every subsequent data extract; however, with increasing data sets per patient this became more and more cumbersome. Rather than continuing with further patches and repairs, we decided to have the database in important parts reprogrammed. This new database became available in January 2019, and until the end of 2019, 21 new participants have been enrolled. All patients enrolled before end 2018 were carried on in the old database. Full migration of their whole datasets into the new database is planned for April - June 2020. The old database will be always open to be consulted, but from July - August 2020 each site can entry data ONLY in the new database. For doubts or questions, please contact us: [support@ttpregistry.net](mailto:support@ttpregistry.net).

## NEW STUDY SITES

In 2019, we opened new study sites in Leipzig and Mainz (Germany) and in Worcester and Oklahoma (USA). Until the end of 2019, we had study sites in 18 different countries.

## DATA COLLECTION AND MONITORING VISITS IN VIENNA AND WARSAW

On 16<sup>th</sup> May 2019 Anette van Dorland and Erika Tarasco visited the study site at Vienna General Hospital in Austria to assist Prof. Paul Knöbl in the collection and completion of baseline and follow-up data of his nine patients.

In July 2019 Erika Tarasco and Isabella Aebi-Huber travelled to the Institute of Hematology and Transfusion in Warsaw, Poland to assist Prof. J. Windyga and Dr. M. Górcka-Kosicka in collecting data for the yearly follow-up of their Registry patients. Erika and Isabella visited the site in Warsaw in company of Dr. Katarzyna Jalowiec, a native Polish speaker and fellow in hematology at the Department of Hematology and Central Hematology Laboratory, Bern University Hospital. During their stay, they collected and updated data of 17 patients.

## AVAILABLE FOLLOW-UP DATA

By the end of 2019, we had at least one follow-up visit reported, or an end-form visit for 87 confirmed patients. These 87 patients had a median follow-up of 4.1 years (range 0-15 years) and a median of three follow-ups per patient (range 0-9 follow-up). This amounts to nearly 400 prospective patient-years. The gap between two visits was 0-1 year in 11 %, and 1-2 years in 53 % of patients. Only 14 % of patients had a gap of more than 3 years.

To further strengthen our data set, we will again focus on prospective data of regular follow-up visits in 2020. If necessary, we will call sites, perform monitoring and support visits to the sites with larger numbers of patients. In addition, we have allocated resources to the team at the University of Oklahoma, who will carry out some of these tasks for patients in the US.

## PUBLICATION IN THE NEW ENGLAND JOURNAL OF MEDICINE

Johanna A. Kremer Hovinga and James N. George were invited by *The New England Journal of Medicine* to write a review article on hereditary TTP, which was published on October 24, 2019. If you want to read this publication, you can click [here](#).

## PUBLICATION IN HAEMATOLOGICA

Accepted in February 2019 by *Haematologica*, appearing finally in print in October 2019 after years of work, was the first major publication from the Registry on 123 hTTP cases, enrolled between 2006 and end of 2017. The systematic collection of clinical data of individual patients revealed substantial comorbidities present at enrollment. Most notable was a high prevalence of premature arterial thromboembolic events, mainly transient ischemic attacks, ischemic strokes, and myocardial infarctions. To read this article entitled “The International Hereditary Thrombotic Thrombocytopenic Purpura Registry: key findings at enrollment until 2017” you can click [here](#).

This publication together with the hereditary TTP Registry project received the Günter Landbeck Excellence Award 2019. The Günter Landbeck Excellence Award is presented annually in Hamburg (Germany), during the Hemophilia Symposium, which celebrated its 50<sup>th</sup> anniversary in 2019. The award lecture was given by Johanna.

## PRESENTATIONS

There were a number of lectures and oral communications on the hereditary TTP Registry in 2019. Examples of this activity are the following abstract presentations:

At the 63<sup>th</sup> Annual Meeting of the Society on Thrombosis and Hemostasis Research (GTH) in Berlin 27 February – 02 March 2019, Anette van Dorland presented the abstract “More severe ADAMTS13 deficiency in homozygous versus compound heterozygous carriers of the ADAMTS13 c.4143\_4144dupA mutation in congenital Thrombotic Thrombocytopenic Purpura (cTTP): Impact on disease onset?” as oral communication.

During the 27<sup>th</sup> Annual Meeting of the International Society of Thrombosis and Hemostasis (ISTH) in Melbourne 06 – 10 July 2019, Erika Tarasco had an oral communication entitled “Age at first disease manifestation in relation to residual ADAMTS13 activity in patients with congenital thrombotic thrombocytopenic purpura”.

Preceding the ISTH congress in Melbourne a special Symposium on Thrombotic Microangiopathies was held on July 5, 2019. In a workshop format, Erika Tarasco presented structural data of the Registry (title: “The international Hereditary TTP Registry: Opportunities and Challenges”). She had a similar talk during the Hemophilia symposium in Hamburg on November 8, 2019.

## THANK YOU!

The whole study team in Bern would like to say “Thank you” for your ongoing support to the Registry.

We would especially like to thank all the patients and their family members for their participation. Without their participation and support, we cannot gain further insights into the hereditary form of TTP, nor help increase awareness for this rare disease.

The study team Bern

Erika Tarasco

Isabella Aebi-Huber