Patient information regarding the study titled

‘‘Phenotype and genotype correlations in hereditary TTP *(Upshaw-Schulman Syndrome)”*

Dear Patient:

1. General information about the study

Thrombotic-thrombocytopenic purpura (abbreviated **TTP**) is a rare disease that is caused by the occurrence of blood clots (so-called blood platelet thrombi) in small and the smallest blood vessels. Blockage of vessels leads to lesions in the affected organs as a result of which stroke, kidney dysfunction, etc. can arise. If left untreated, the disease leads to death in 90% of cases.

For the most part we now distinguish between two forms, acquired TTP and congenital (= hereditary or familial) TTP. The congenital form is also called **Upshaw-Schulman Syndrome**, having been named after those who first described it. Upshaw-Schulman Syndrome is caused by genetic defects (mutations) in the ADAMTS13 (= Von Willebrand factor-cleaving protease) gene. This results in functional ADAMTS13 no longer being able to be formed. Hence, ADAMTS13 activity that can be measured in plasma of Upshaw-Schulman Syndrome patients amounts to less than 5% of normal levels.

Various case reports about individual patients have been published since the Von Willebrand factor-cleaving protease (ADAMTS13) and the connection between a serious ADAMTS13 deficiency and TTP have been discovered. Based on this, we estimate that there are currently approximately 150 known Upshaw-Schulman in the world. Unfortunately, since too little is known about Upshaw-Schulman Syndrome at this time, the disease is often diagnosed too late or not at all and many patients or their siblings have either died or suffered extremely serious, permanent organ damage from it. This is all the more unfortunate since acute TTP episodes in Upshaw-Schulman Syndrome patients can be successfully treated with simple plasma infusions. Today, there are numerous patients receiving plasma infusions every 2-3 weeks to prevent recurring episodes and living normal lives. These days the question remains open as to whether all patients should receive this type of preventative treatment, or perhaps certain specific situations warrant the use of some other therapy that may not be as effective in reducing the risk of an episode’s occurring. (And what would these specific situations be?)

2. Goal of the study

The goal of the study is to gather as much information as precisely as possible concerning the course of illness, factors that may trigger episodes (i.e. pregnancy, infections, etc.), plasma therapy and other treatments from as many patients with Upshaw-Schulman Syndrome as possible. During a second step, the information gathered is to be used in development recommendations on therapies. Since it seems possible that the clinical course is influenced by genetic factors (e.g. the ADAMTS13 mutations, Von Willebrand factor-mirror, etc., as the case may be), familial factors, or event transient and environmental factors (taking medications, pregnancy, etc.), these factors will be investigated using a questionnaire, laboratory studies, and studies on family members.

The long-term goal of the study is to build a network, including a knowledge platform, to exchange experiences on therapy, on the occurrence of side-effects during treatment, and on long-term progress, thereby improving treatment and prevention for affected patients. Treating physicians and affected patients will have access to the knowledge platform.

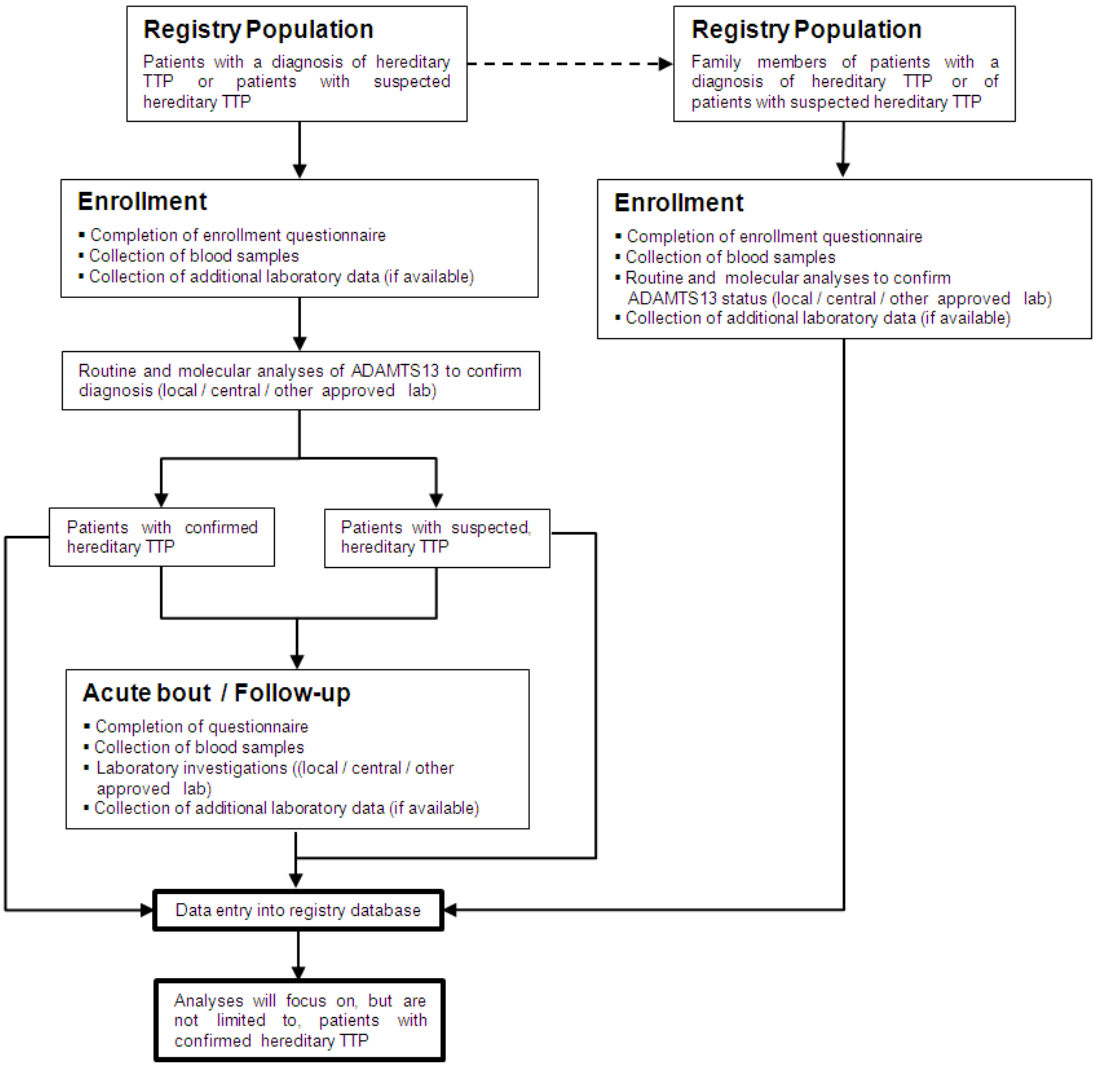
3. Selection of study participants

You were asked to participate in the study because you have been diagnosed with the familial form of thrombotic-thrombocytopenic purpura, also as the Upshaw-Schulman Syndrome. Members of your family will also be asked to participate in this study. Unlike you, they will only be interviewed and examined once (see diagram below).

4. Voluntary participation

Your participation in this study is voluntary. Should you decline to participate in this study, there will be no negative effect on the medical care you receive. The same is true if you withdraw your consent to participate at a later point in time. You may do this at any time. You do not need to provide any reason for retracting your consent or withdrawing from the study.

5. Study schedule



At the beginning of the study, your doctor will fill out a (basic) questionnaire with you and, if needed, take a blood sample. Later, your doctor will fill out a yearly follow-up questionnaire with you and, if necessary, take a blood sample. If you experience episode of your illness, your doctor will fill out a questionnaire with you and, if needed, take a blood sample.

The plan is to document the course of your illness over several years and to store the data in the Upshaw-Schulman Syndrome registry.

6. Responsibilities of the study participants

As a participant in the study, you have the obligation to adhere to the study plan and to provide your physician exact information about the course of your illness, any concomitant treatment by another doctor, any medications you are taking (whether with a doctor's prescription or over the counter), and any adverse effects you experience.

7. Benefit to participants

Participating in this study will benefit you in that, over time, recommendations based on the evidence will become available regarding my treatment, measures in specific risk situations, or a regular plasma prophylaxis. Thanks to your participation in the study, the results will also benefit other persons afflicted with this condition.

8. Risks and discomforts

The only discomfort from participating in this study is from the normal drawing of blood, which is done once a year (and, for family member, only once upon entering the study). Drawing blood is never completely pain-free because of the needle. Problems associated with drawing blood sometimes include bruising in the location where the needle was inserted, which could become infected in very rare cases.

The collected blood samples are examined and subsequently deep-frozen. They will be kept deep-frozen for possible later examination, including genetic analyses, connected with the research into Upshaw-Schulman Syndrome. If your participation in the study is terminated, the frozen samples will be destroyed. However, the data and information collected up until that time will not be deleted.

9. New knowledge

The lead investigator will regularly inform your physician about the progress of the study and any new knowledge that has been obtained. Your physician will pass this information along to you. In addition, you will have access to the information on the website. Of course, you also have the right not to know; that is we will not force you to receive this information.

10. Data confidentiality

During this study, personal data relating to you, such as your name, date of birth, gender, and medical data, will be collected in connection with Upshaw-Schulman Syndrome and will be retained at the study centre (University Hematology Clinic, Inselspital, Bern, Switzerland). With the exception of your name, these data will be saved in a database specifically created for this purpose (Upshaw-Schulman Syndrome Registry). The data (exclusive of your name) will be sent to the Clinical Trials Unit (CTU), Inselspital, Bern University Hospital, CH-3010 Bern, Switzerland for data processing. Your doctor, specialists at the study centre in Bern, professionals at CTU responsible for processing the data, and individuals appointed by it, will have access to the data in the database. Additional individuals domestically and abroad may access the data (except for your name) in order to research Upshaw-Schulman or to develop therapy guidelines. Members of the Bern Cantonal Ethics Commission and members of the Bern Canton Data Protection Oversight Department may have access to the data as part of inspections. Confidentiality will be maintained throughout the entire study and whilst the referenced oversight controls are being performed. Under no circumstances will your name be published in any reports or publications resulting from the study.

11. Compensation for participating in the study

Study participants will not receive remuneration. Regular basic tests such as blood count, kidney function, etc. are indicated because of your illness and do not need to be performed again for the study. Any extra tests that are scheduled are free of charge. Neither you nor your health insurance company will incur any additional costs as a result of your participation.

12. Financing for the study

This study is financed through third party funds (grants from the Swiss National Fund (SNF) and the Swiss Mach-Gaensslen Foundation).
Since August 2008, additional support has been obtained from Baxter Innovations GmbH in Vienna, Austria.

13. Contact person(s)

Please contact your treating physician or the lead investigator shown below, if there is anything that is unclear to you or if you should have any questions over the course of the study.

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Statement of informed consent for research study and registration of my history of illness as part of the study titled *"Phenotype and genotype correlation in hereditary TTP (Upshaw-Schulman Syndrome)"*

Patient:

Surname: ..... First name: .....

Date of birth: ..... Gender: .....

Investigator:

Surname: ..... First name: .....

- My physician has informed me about the sequence and purpose of the study titled *"Phenotype and genotype correlation in hereditary TTP (Upshaw-Schulman Syndrome)"*. I have obtained, read, and understood the patient information provided for the study. Furthermore, any questions I have had relating to participation in this study have been answered to my satisfaction.
- I had sufficient time to arrive at my decision to participate in this study voluntarily.
- I will receive a copy of the patient information and will receive a copy of the signed informed consent statement.
- I have been informed about the scientific investigations regarding genes, proteins, or other factors, which will be conducted as part of the study in question.
- As part of this study, I give my consent that any blood that is taken for the study to be stored for an undetermined period of time, and likely several years, at the study centre (University Hematology Clinic, Inselspital, Bern) and that it may be used for additional scientific investigations. These investigations will serve to better understand congenital ADAMTS13 deficiency / hereditary TTP (Upshaw-Schulman Syndrome) and/or to improve the diagnosis and treatment of future patients who have this or a similar illness.
- As part of this study, I give my consent for (i) personal data, such as name, date of birth, gender, and medical data to be collected in connection with Upshaw-Schulman Syndrome and stored at the study centre (University Hematology Clinic, Inselspital, Bern); (ii) for this information to be sent to the Clinical Trials Unit (CTU), Inselspital Bern University Hospital, CH-3010 Bern, Switzerland for the purpose of data processing; (iii) for my physician, specialists at the Bern study centre, specialists of the CTU Bern responsible for data processing, and persons appointed by the CTU to have access to my stored data; (iv) for this information, except for the name, to be accessed by additional individuals domestically and abroad as part of research into Upshaw-Schulman Syndrome and to develop treatment guidelines; (v) for domestic authorities to be able to access my data.
- I understand and accept that the regulations of other countries governing data protection are not necessarily consistent with those of Switzerland. Confidentiality will be protected.
- In the event of publication (in a professional journal, or on the Upshaw-Schulman website of the University Hematology Clinic, Inselspital, Bern), all data will be rendered anonymous and coded such that my personal identity cannot be discerned.
- Participating in this study will benefit me in that, over time, recommendations based on the evidence will become available regarding my treatment, measures in specific risk situations, or a regular plasma prophylaxis.
- I may withdraw my consent to participate at any time without providing any reason and without there being any negative impact on me or my family members. In the event my participation in the study is terminated, any bloods samples that have been taken from me and are still in storage will be destroyed. The collected data, however, will not be deleted.
- Neither I nor my family members will incur any costs for participating in this study. However, I also have no entitlement to financial compensation.
- My physician will receive the results of the investigations performed and will discuss them with me. He/she will be regularly informed about progress made in the study and about developments in the area of hereditary TTP (Upshaw-Schulman Syndrome).

Location, Date..... Patient Signature.....

Location, Date..... Signature of Investigator.....