University of Pittsburgh

CONSENT TO ACT AS A SUBJECT IN A RESEARCH STUDY

TITLE: Prospective, Randomized, Crossover Trial Comparing Recombinant von Willebrand Factor (rVWF) vs. Tranexamic Acid (TA) to Minimize Menorrhagia in Women with von Willebrand Disease: The VWD Minimize Study

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Why is this research being done?

The purpose of this research study is to compare the use of recombinant von Willebrand factor (rVWF) and tranexamic acid (TA, Lysteda®) in women with von Willebrand Disease (VWD) who have heavy monthly periods (also called menorrhagia). Von Willebrand disease is a common bleeding disorder genetic trait passed on in families (or inherited) that occurs in 1% of the population. It is caused by deficient or defective von Willebrand factor (VWF). Most people with VWD are treated with DDAVP (desmopressin), which is a protein given by vein or as an intranasal spray to treat bleeding symptoms. The problem is that some patients do not respond to DDAVP, or the response may be limited. This is because after three days, the stores of VWF become low (or depleted). Tranexamic acid is another treatment for menorrhagia, but it is less effective than DDAVP. Thus better treatments are needed for individuals with VWD.

In two clinical trials, rVWF has been shown to be safe and effective in treating and preventing bleeds in patients with VWD. Among women with menorrhagia in those trials, it also reduced menstrual bleeding. rVWF is approved by the U.S. Food and Drug Administration (FDA) for the treatment and prevention of bleeding in adults. It has been safely used off-label in children as standard practice by many clinicians.

In the studies above, rVWF was given by intravenous (in a vein) infusion, reduced bleeding, and was safe and well-tolerated. In a survey of 16 hemophilia treatment centers, VWF concentrate has been used for menorrhagia only after first and second line treatments fail: in all 13 subjects receiving VWF there was reduction in heavy menstrual bleeding. In six published studies of rVWF or plasma-derived (pd) VWF concentrate, including two prospective, two retrospective and two observational studies of 455 VWD subjects, a total of 88 women received VWF 36-50 IU/kg for 1-6 days with reduction in menstrual bleeding in all women, and no adverse effects. Tranexamic acid (Lysteda®) in this study is taken as a pill by mouth three times daily. It is approved by the FDA for the treatment of menorrhagia in children and adults.

Who is being asked to participate in this research study?
Your daughter is being asked to participate in this research study because your daughter is a woman 13 to 18 years of age with VWD and your daughter has heavy periods. Your daughter cannot participate is your daughter is pregnant or lactating or if your daughter is not willing to use a "double-barrier" method of contraception during the study. Your daughter must also be willing to avoid aspirin and nonsteroidal anti-inflammatory drugs, e.g. ibuprofen, during study. This site is one of approximately 25 sites in the United States and hopes to screen 20 subjects in order to enroll a total of 17-19 subjects (66 total subjects for the entire study). Your daughter's participation will last approximately 24 weeks (6 months). The projected duration of the study at all sites is expected to be around 5 years.

What procedures will be performed for research purposes?
If your daughter decides to participate in this study, your daughter will sign a consent form. This is a 24-week outpatient study that involves 4 visits. There are 3 parts to the study: pre-treatment, treatment, and post-treatment (described in detail below and in an appendix chart located end of this consent form). The study involves two treatment arms, Arms A and B, in which your daughter will receive two drugs, one given by intravenous injection and one given orally. This study is called a "prospective randomized, crossover study" which means your daughter will receive both treatment arms, but neither your daughter nor your daughter's study doctor (or staff) will choose the order of the treatment arms.

If your daughter agrees to participate, your daughter will be randomized (like a toss of a coin) to be in Group I or Group II for the first 5 days of menstrual bleeding in your daughter's next four consecutive menstrual cycles. There is an even (50/50) chance that your daughter will be assigned first to either Group I or Group II treatment, as described here. If your daughter is in **Group I**, your daughter will receive **Arm A** for menstrual bleeding in cycles 1 and 2, followed by **Arm B** for menstrual bleeding in cycles 3 and 4. If your daughter is in **Group II**, your daughter will receive **Arm B** for menstrual bleeding in cycles 1 and 2, followed by **Arm A** for menstrual bleeding in cycles 3 and 4 (See Table below).

Group	**Cycles 1, 2**	**Cycles 3, 4**
Group I	**Arm A**: rVWF 40 IU/kg day 1	**Arm B**: TA 1300 mg po tid days 1-5
Group II	**Arm B**: TA 1300 mg po tid days 1-5	**Arm A**: rVWF 40 IU/kg day 1

rVWF is von Willebrand factor concentrate; TA is tranexamic acid; tid is three times daily; po is orally.

If your daughter is in **Group I**, your daughter will receive Arm A first: rVWF 40 IU/kg by intravenous injection on day 1 of menstrual bleeding in each of your daughter's next two menstrual cycles, "cycles 1 and 2." Then, your daughter will crossover (switch) to receive Arm B: TA by mouth (2 pills which equal 1,300 mg) three times daily (tid) on days 1-5 during the first 5 days of menstrual bleeding in each of your daughter's next two menstrual cycles "cycles 3 and 4."

If your daughter is in **Group II**, your daughter will receive Arm B first: TA by mouth (2 pills which equal 1,300 mg) three times daily (tid) on days 1-5 during the first 5 days of menstrual bleeding in each of your daughter's next two menstrual cycles "cycles 1 and 2." Then your daughter will crossover (switch) to receive Arm A: rVWF 40 IU/kg by intravenous injection on day 1 of menstrual bleeding in each of your daughter's next two menstrual cycles, "cycles 3 and 4." Before your daughter starts the study drugs, your daughter will have a brief medical history,

physical exam, and blood tests to check for thyroid function and iron deficiency. The HCWP nurses will also train your daughter to give the rVWF infusion, but if your daughter prefers a visiting nurse (OPTION CARE) to give rVWF in your home, that can be arranged. During your daughter's next 4 monthly menstrual cycles (periods) your daughter will receive rVWF alone for two cycles **AND** TA alone for two cycles, the order of which will be decided by randomization. These drugs can be taken in your home, or your daughter can come into the center for the rVWF infusion.

There will be a total of 4 visits for outpatient monitoring by the Hemophilia Center of Western PA (HCWP). The drugs used in this study will be supplied by an NIH-contracted pharmacy, and shipped to the Hemophilia Center of Western PA. Your daughter's study drugs will be provided in a special kit for each cycle, which will be reviewed with the study nurse so your daughter is completely familiar with the contents and how and when to take the study drug each cycle. The nurse will also provide your daughter with a supply of tampons and pads, which your daughter will use exclusively (no other tampons or pads will be permitted) during the study.

Study Visit 1: Screening Procedures, Week 0
To determine if your daughter is eligible to take part in this study, your daughter will have the following procedures performed:

- Review of informed consent: Dr. Ragni will review this document and answer any of your daughter's questions. If your daughter decides to participate in the study, your daughter will be asked to sign this informed consent document. A copy will be given to your daughter for your daughter's records.
- Demographics and medical history: your daughter's age, bleeding history, surgical history, any prescription and non-prescription drugs your daughter is taking, and review of medical problems
- Physical examination and vitals will be taken: Including height, weight, blood pressure, respirations, temperature, pulse
- Your daughter will also be asked about the bleeding severity during your daughter's last 2 menstrual cycles.
- Your daughter will be asked to fill out 4 Quality-of-Life questionnaires (answering questions about how your daughter is feeling, your daughter's daily activities, and bleeding).
- Urine pregnancy test
- Blood Draw: your daughter will have ~1¾ tablespoon (~28 ml) of blood drawn for the following tests:
    - Blood Counts: hemoglobin, platelet count
    - Iron Tests: Iron, total iron blinding capacity (TIBC), and ferritin.
    - Thyroid Test: Thyroid stimulating hormone (TSH) to test thyroid function.
    - Von Willebrand Tests: von Willebrand factor (VWF) tests and genotype.

Dr. Ragni and her staff will review your daughter's past clinical and laboratory records to verify your daughter has von Willebrand disease, which will be documented for research purposes. This one time visit will take about 2 hours. The Blood Count Tests, Iron Tests and Thyroid Test

will be run by Quest Diagnostics in Pittsburgh, Pennsylvania. The von Willebrand Tests will be performed at the Francis Owen Blood Research Laboratory, in Chapel Hill, North Carolina, and genotype will be run at Functional Bioscience, Madison WI.

Study Visit 2: Before Menstrual Cycle 1, Week 4
The study nurse will contact your daughter within a few days of screening to let your daughter know if your daughter is eligible or not. If your daughter is not eligible, this will end your daughter's participation and your daughter will not go on to receive study drug. If it is determined your daughter is eligible to participate, your daughter will be randomized to either Study Group I or Study Group II. All visits will be at the Hemophilia Center of Western Pennsylvania. The study nurse will also schedule your daughter's next appointment for your daughter within the next few weeks.

> **Group I:** Your daughter will start with **Arm A:** Your daughter will take rVWF on day 1 of the next two monthly menstrual cycles (Cycles 1 and 2). This will be followed by **Arm B**: Your daughter will take TA for the first 5 days during the next two monthly menstrual cycles (Cycles 3 and 4).
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> **Group II:** Your daughter will start with **Arm B:** Your daughter will take TA for the first 5 days during the next two monthly menstrual cycles (Cycles 1 and 2). This will be followed by **Arm A:** Your daughter will take rVWF on day 1 of the next two monthly menstrual cycles (Cycles 3 and 4).

At home, on day 1 of each of your daughter's next four menstrual cycles, your daughter will perform a home pregnancy test (to make sure your daughter is not pregnant). If the test indicates your daughter is not pregnant, your daughter may begin taking their study drug, either rVWF alone or TA alone. If your daughter is not able to come to clinic or set up an OPTION CARE visit to administer rVWF on day 1 of the cycle to which your daughter is assigned, your daughter should notify your daughter's nurse, and plan to come in to HCWP or schedule OPTION CARE on Day 2. If your daughter's bleeding is not relieved after one dose of rVWF, your daughter's HTC doctor may give an additional dose of rVWF on the following day.

If your daughter is assigned to rVWF, it is preferable that your daughter take it in the morning, if possible. When your daughter takes TA, it is preferable that your daughter takes the first of your daughter's TA pills by mouth around 8:00 AM (at breakfast). Your daughter may take your daughter's second TA dose with lunch and third TA dose with dinner.

Your daughter will take rVWF for 1 day and TA for 5 days. Your daughter will record the pregnancy test results, menstrual bleeding and symptoms, and when your daughter took the study drug in a diary, and how much your daughter is bleeding in the Pictorial Blood Assessment Chart (PBAC) during each cycle. The diary can be accessed on any computer device (i.e., home computer, tablet computer, etc.) via a secure Internet connection. The HTC staff will train your daughter on how to complete the diary entries and the PBAC score. If your daughter does not have a personal computer, your daughter can complete paper diaries and PBAC entries. Your daughter should call the study nurse coordinator to arrange your daughter's next visit and address any questions your daughter may have. If at any time during this study, there are changes in your daughter's health or need to take any type new medication, you should call someone on the study team.

- Your daughter will be given a supply of study drugs to take during bleeding on your daughter's next 4 menstrual cycles, including Cycles 1, 2 (either rVWF alone **OR** TA

alone) and Cycles 3, 4 (either TA alone OR rVWF alone).

- Your daughter's study nurse coordinator will review how and when your daughter will administer study drug. If your daughter chooses to use a visiting nurse for rVWF infusion, this will be set up for your daughter.

- Your daughter will be given access to complete the diary computer forms, or the paper copies will be provided for the diary and PBAC chart; and your daughter will be given home urine pregnancy tests. Your daughter will review their use with the study nurse coordinator. The urine pregnancy test will be done at the onset of menses each cycle (cycle 1, 2, 3, 4) *before* your daughter takes the study drugs.

Your daughter will have 2 additional visits at the Hemophilia Center of Western PA. Dr. Ragni and study nurse will meet your daughter there. The purpose of these visits is to (1) review the study drug (2) test your daughter's quality of life, and (3) review your daughter's menstrual bleeding severity using the PBAC chart. Each of these visits will last approximately 1 hour.

Study Visit 3: Before Menstrual Cycle 3, Week 16
At home, on day 1 of each of your daughter's next menstrual cycles, your daughter will perform a home pregnancy test (to make sure your daughter is not pregnant). If the test indicates your daughter is not pregnant, your daughter may begin taking your daughter's study drug, either rVWF alone or TA alone. If your daughter is not able to come to clinic or set up an OPTION CARE visit to administer take rVWF on day 1 of the cycle to which your daughter is assigned, your daughter should notify her nurse, and plan to come in to HCWP or schedule OPTION CARE on Day 2. If your daughter's bleeding is not relieved after one dose of rVWF, your daughter's HTC doctor may give an additional dose of rVWF on the following day.

If your daughter is assigned to rVWF, it is preferable that your daughter take it in the morning, if possible. When your daughter takes TA, it is preferable that your daughter take the first of your daughter's TA pills by mouth around 8:00 AM (at breakfast). Your daughter may take her second TA dose with lunch and third TA dose with dinner.

Your daughter will continue your daughter's assigned drug(s) as directed. Your daughter will complete the PBAC and diary, either via computer access or in paper format. Your daughter should call the study nurse coordinator to arrange your daughter's next visit and address any questions your daughter may have. If at any time during this study, there are changes in your daughter's health or need to take any type new medication, your daughter should call someone on the study team.

- Your daughter will review the study drugs to take during bleeding on your daughter's next 2 menstrual cycles, Cycles 3, 4 (either rVWF alone **OR** TA alone).

- Your daughter's study nurse coordinator will review how and when your daughter will administer study drug. If your daughter chooses to use a visiting nurse for rVWF infusion, this will be set up for your daughter.

- Your daughter will review your daughter's diary entries, urine pregnancy tests, and PBAC chart with the study nurse coordinator. The urine pregnancy test will be done at the onset of menses for each cycle *before* your daughter takes the study drugs.

- Your daughter will be asked to fill out 4 Quality-of-Life questionnaires (answering questions about how your daughter is feeling, your daughter's daily activities, and bleeding), a satisfaction survey, and a cost-effectiveness questionnaire.

Study Visit 4: After Menstrual Cycle 4, End-Study Visit, Week 24
The final visit will be at the Hemophilia Center of Western PA. This visit will last approximately 1 hour where your daughter will have the following procedures performed:

- Vital signs.
- Your daughter will be asked how your daughter has been doing since your daughter's last visit (including any problems and any medications your daughter is taking).
- A medical history will be performed by the physician or study nurse.
- Your daughter diary entries, urine pregnancy test results, PBAC chart, and cycle severity score will be reviewed by the study nurse coordinator.
- Quality-of-Life questionnaires, a satisfaction survey, and a cost-effectiveness questionnaire will be completed.
- Unused study drugs will be collected.

This will complete your daughter's study participation.

Total Blood Draw
The total blood draw during this 24-week study is approximately 1¾ tablespoon (or 28 ml).

Blood Sample and Data Storage
As part of this study, we are obtaining data and blood samples from your daughter. We would like to use this data and blood for this study. Your daughter's samples will be labeled with code numbers, and information linking the code numbers to your daughter's identity will be kept in a separate, locked file at the Hemophilia Center. Your daughter's von Willebrand Test blood samples will be stored indefinitely at the Francis Owen Blood Research Laboratory, University of North Carolina, and under the control of Dr. Nichols and Dr. Ragni. Dr. Nichols is engaged in von Willebrand Disease research. There is no plan at this time to share your daughter's data and samples outside of this study. Any request to share your daughter's data and samples with other researchers outside of this study must be approved in a formal application process with the NIH. Your daughter's samples will most likely be used up in the von Willebrand factor (VWF) and genotype testing, but leftover samples will be stored indefinitely unless your daughter does not wish to have their samples stored.

If future testing is approved by the NIH for other research studies, this may provide additional information that will be helpful in understanding von Willebrand disease or other diseases or conditions, including research to develop investigational tests, treatments, drugs or devices that are not yet approved by the U.S. Food and Drug Administration. It is unlikely that what we learn from these studies will have a direct benefit to your daughter. There are no plans to provide financial compensation to your daughter should this occur. By allowing us to use your daughter's data and blood your daughter gives up any property rights your daughter may have in the data and blood samples.

We will only share your daughter's data and blood samples with other researchers if the NIH approves this action via the formal application process described above. They may be doing research in areas similar to this research or in other unrelated areas. These researchers may be at the University of Pittsburgh, at other research centers and institutions, or industry sponsors of research. We may also share your daughter's research data with large data repositories (a repository is a database of information) for broad sharing with the research community. If your daughter's individual research data is placed in one of these repositories, only qualified researchers who have received prior approval from individuals that monitor the use of the data will be able to look at your daughter's information.

If your daughter changes her mind and does not want us to store and use your daughter's data and blood samples for future research your daughter should contact the research team member identified at the top of this document. The data and blood samples will no longer be used for research purposes. However, if some research with your daughter 's data and blood samples has already been completed, the information from that research may still be used. Also, if the data and blood has been shared with other researchers it might not be possible to withdraw the data and blood to the extent it has been shared.

What are the possible risks, side effects, and discomforts of this research study?
As with any investigational study, there may be adverse events or side effects that are currently unknown and it is possible that certain of these unknown risks could be permanent, serious, or life-threatening. There may be risks and discomforts associated with these products and study treatment that are not yet known at this time. Should your daughter encounter any side effects your daughter think might be related to this study or the drugs, your daughter should contact Dr. Ragni immediately.

Risk of Blood Drawing
There may be discomfort with drawing blood, which is common, and may include pain, lightheadedness bruising, or bleeding or infection in the tissue around the vein. This may be alleviated or reduced by applying pressure to the blood draw site for 5 minutes, and by lying on your daughter's back with your daughter's head flat and knees bent if your daughter feels lightheaded. The risk of repeated blood draws is anemia, or a low blood count, but this will be carefully monitored. Injections may rarely cause pain, soreness, redness, warmth, itching, numbness, tenderness, swelling, skin changes (discoloration, breakdown, or thickening), or swelling or lymph nodes near the injection site.

Risk of Inadvertent Disclosure
There is a possibility that if the result of the research studies involving your daughter's medical record or genetic material were to become generally known, this information could impact future insurability, employability, or reproduction plans, or have a negative impact on family relationships, and/or result in paternity suits or stigmatization (identifying as unusual, different).

Risk of Allergic Reaction
An allergic reaction to study treatment with rVWF may rarely occur, in less than 0.001% or 1 in 100,000 people, and could cause in decreasing order of severity: death, anaphylaxis, which is a life-threatening reaction causing difficulty breathing, low blood pressure and irregularity of the heartbeat, hypervolemia (overabundance of body fluid), paresthesias (prickling sensation), urticaria (hives) generalized or localized to the injection site, chest tightness, rash, pruritus (itching), and/or edema (swelling), fever, and chills. The dose chosen for the study, 40 IU/kg, appears to be safe and well tolerated in clinical trials.

An allergic reaction to treatment with TA is rare. Symptoms may include chills, fever, nausea and vomiting, or rarely may include in decreasing order of severity: death, anaphylaxis, which is a life-threatening reaction causing difficulty breathing, low blood pressure, heart irregularity, increase in body fluids, paresthesias (numbness or pricking sensation), urticaria (hives), chest tightness, rash, pruritus (itching), edema (swelling), fever, and/or chills. Should this occur, Benadryl, a medication which reduces inflammation, may be given, with close monitoring of these symptoms. Benadryl may cause drowsiness, dizziness or low blood pressure. Your daughter will be monitored for these symptoms while receiving drugs.

No one with a known allergy to either rVWF or TA will be enrolled in this study.

Risk of Thromboembolism

Although rVWF and TA increase blood protein levels, there is the rare possibility that rVWF or TA could cause a clot in the vein (thrombosis) with swelling, pain, or a clot in the lung (pulmonary embolus) with shortness of breath or coughing up blood. This risk will be very carefully monitored clinically. The use of oral contraceptives with TA may increase risk of venous thromboembolism, and thus will not be allowed during study. Should these symptoms occur; measures considered standard of care would be implemented to prevent clots: these include either compression stockings, which are support-like stockings, and/or sequential compression devices (SCDs). SCDs are blanket-like Velcro-devices which are placed on the legs to promote blood flow and prevent clots from forming in the leg veins. Treatment, should a clot occur, would primarily consist of stopping the study product as soon as possible. If needed, the risks and benefits of anticoagulation will be considered.

Risk of Bleeding Events

Bleeding symptoms may occur in VWD unrelated to this study, usually with trauma, but sometimes spontaneously, without cause. Although unlikely, if your daughter has bleeding, or if your daughter has menstrual bleeding not controlled after five days with study drugs, standard treatment, DDAVP or factor concentrate whichever your daughter usually uses, will be given.

Risk of Pregnancy

rVWF has not been studied in pregnant women. Thus, it is recommended that pregnancy should be avoided in subjects on this study. Avoiding sexual activity is the only certain method to prevent pregnancy. However, if your daughter chooses to be sexually active, your daughter must agree to use an appropriate double barrier method of birth control, such as female use of a diaphragm, intrauterine device (IUD), sponge and spermicide, in addition to the male use of a condom. The double barrier contraception must be used for at least one week prior to the start of the research study and continue for at least two weeks following the last study visit. If your daughter chooses to be sexually active during this study, your daughter must accept the risk that pregnancy could still result, exposing your daughter and your daughter's sexual partner to potential loss of pregnancy as well as other unknown effects on the developing fetus.

Birth Control Statement

If your daughter becomes aware that she is pregnant or becomes pregnant during the course of this research study, your daughter must contact the principal investigator and physician immediately. The effects of rVWF on the fetus (unborn daughter) are not fully known. It is therefore important that your daughter does not become pregnant during this research study. Your daughter should not use hormones or a birth control implant during this study because of thrombosis (clot) risk. Double barrier contraception must be used for at least one week prior to the start of the research study and continue for at least two weeks following the last study visit.

Breach of confidentiality
There is also a potential for possible risk of breach of confidentiality of collected information. To minimize this risk, your daughter's study participation and related information will be protected to maintain confidentiality. Your daughter's blood samples and clinical history will be assigned an alphanumeric identifier and the key for linking this number with your daughter's identity will be kept at HCWP under lock and key by Dr. Ragni and her research staff. The de-identified information in this study will be placed into a secure, web-based data base at University of Pittsburgh Center for Research in Health Care Data Center (CRHC DC). If the investigator publishes research information, your name will not be identified.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by US Law. This website will not include information that can identify your daughter. At most, the website will include a summary of the results. Your daughter can search this website at any time.

What are the possible benefits from taking part in this study?
It is possible that rVWF and/or TA will reduce your daughter's heavy menstrual bleeding. However, there is no guarantee that your daughter will receive such a benefit. If the information gathered from the use of rVWF and/or TA during menstrual periods, including reducing bleeding and increasing von Willebrand tests (VWF and related factors), then this may provide important information for the future use of rVWF and/or TA for bleeding in individuals with VWD, when standard therapy is inadequate.

What treatments or procedures are available if my daughter decide not to take part in this research study?
If your daughter chooses not to participate in this study, your daughter understands that your daughter will receive the usual medical care appropriate for your daughter's condition. your daughter will receive DDAVP or available VWF clotting factor if your daughter were to have bleeding or surgery or procedures. TA (Lysteda®) is commonly prescribed for women without VWD for menorrhagia.

If my daughter agrees to take part in this research study, will my daughter be told of any new risks that may be found during the course of the study?
If new information becomes available during your participation in this study that may influence your daughter's willingness to participate, your daughter's doctor will communicate this to your daughter promptly.

Will my daughter's insurance provider or my daughter be charged for the costs of any procedures performed as part of this research study?
All procedures associated with this study are for research, including laboratory tests, out-patient hospitalization, study drugs, drug injections, and blood sampling. Neither your daughter nor your daughter's insurer will be billed for any research-only services. The study drugs have been provided by pharmaceuticals that manufacture the drugs and their distribution will be covered by a grant from the National Institutes of Health to the University of Pittsburgh and Dr. Ragni. Your daughter will be responsible for any routine medical care not part of this experimental study, should such costs arise. The cost of DDAVP or clotting factor, should they be needed, is considered standard of care, and your daughter or your daughter's third-party payer will be responsible for associated costs. Your daughter will be responsible for any applicable co-pays, coinsurances and deductibles.

Will my daughter be paid if my daughter takes part in this research study?
Your daughter will be compensated $100.00 for each visit, for a total of $400.00 if your daughter completes all parts of this study. If, for whatever reason, your daughter completes part but not all of

the study, the terms of this payment will be $100 for completing the initial Screening (visit 1); and $100 per visit for the 3 study visits 2-4. your daughter will not be compensated for any additional visits. Your daughter will be paid only after your daughter completes all visits for the study. Please allow 4-6 weeks.

Your daughter will be paid on a reloadable debit card. All compensation is taxable income to the participant regardless of the amount. If you receive $600 or more in a calendar year from one organization, that organization is required by law to file a Form 1099 – Miscellaneous with the IRS and provide a copy to the taxpayer. Individuals who do not provide a social security number may still participate in the research, but the IRS requires that 28% of the payment be sent by the institution to the IRS for 'backup withholding;' thus you would only receive 72% of the expected payment.

Who will pay if my daughter is injured as a result of taking part in this study?
If your daughter believes that she is injured as a result of the research procedures being performed, please contact immediately the Principal Investigator listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your daughter's participation in this research study will be provided to your daughter by the hospitals of the UPMC. It is possible that UPMC may bill your daughter's insurance provider for the costs of this emergency treatment, but none of these costs will be charged directly to your daughter. If your daughter's research-related injury requires medical care beyond this emergency treatment, your daughter will be responsible for the costs of this follow-up care unless otherwise specifically stated below. There is no plan for monetary compensation. Your daughter does not, however, waive any legal rights by signing this form.

Will this research study involve the use or disclosure of my daughter 's identifiable medical information?
This research study will involve the recording of current and/or future identifiable medical information from your daughter's hospital and/or other (e.g. physician office) records. The information that will be recorded will be limited to information concerning Blood Counts, Iron Tests, Thyroid Test, and von Willebrand tests your daughter is scheduled to undergo, the results of these tests, and any adverse events associated with testing. This information will be used for the purpose of determining individuals in whom rVWF and TA are effective and for potential treatment for menorrhagia.

This research study will result in identifiable information that will be placed into your daughter's medical records held at the Hemophilia Center. The nature of the identifiable information resulting from your daughter's participation in the research study that will be recorded in your daughter's medical record includes the results of the Blood Counts, Iron Tests, Thyroid Test, and von Willebrand Tests, along with any information related to any adverse events your daughter may suffer during these tests.

Who will have access to identifiable information related to my daughter 's participation in this research study?
In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable medical information related to your daughter's participation in this research study. Authorized representatives of the University of Pittsburgh Office of Research Protections may review your identifiable research information (which may include your daughter's identifiable medical information) for the purpose of monitoring the appropriate conduct of this research study.

In unusual cases, the investigators may be required to release identifiable information (which

may include your daughter's identifiable medical information) related to your daughter's participation in this research study in response to an order from a court of law. If the investigators learn that your daughter or someone with whom your daughter is involved with is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.

Authorized representatives will review and/or obtain identifiable information (which may include your daughter's identifiable medical information) related to your daughter's participation in this research study for the purposes of monitoring the accuracy and completeness of the research data and for performing required scientific analyses of the research data. Your daughter's blood samples will be stored indefinitely at the Francis Owen Blood Research Laboratory, University of North Carolina, and under the control of Dr. Nichols and Dr. Ragni. There is no plan for the samples to undergo other tests or be given to other investigators. If such a plan were considered, your daughter would be re-consented for your daughter's approval. No additional samples will be required than those in the current study. While the study sponsor understands the importance of maintaining the confidentiality of your daughter's identifiable research and medical information, the University of Pittsburgh cannot guarantee the confidentiality of this information after it has been obtained by others.

Authorized representatives of the National Institutes of Health, U.S. Food and Drug Administration may review and/or obtain identifiable information (which may include your daughter's identifiable medical information) related to your daughter's participation in this research study for the purpose of monitoring the accuracy of the research data.

While the external agencies mentioned understand the importance of maintaining the confidentiality of your daughter's identifiable research and medical information, the University of Pittsburgh and HCWP cannot guarantee the confidentiality of this information after it has been obtained by the any external monitoring entity.

Authorized representatives of HCWP and other health care providers may have access to identifiable information (which may include your daughter's identifiable medical information) related to your daughter's participation in this research study for the purpose of (1) fulfilling orders, made by the investigators, for hospitals and health care services (e.g. laboratory tests, diagnostic procedures associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance).

To further protect your daughter's privacy, the investigator has obtained a Certificate of Confidentiality from the federal government. This Certificate may prevent the investigator from being forced (for example by court subpoena) to disclose information that may identify your daughter in any federal, state, or local civil, criminal, administrative, legislative, or other proceeding. However, a Certificate of Confidentiality does not prohibit the investigator from disclosing information about your daughter or your daughter's involvement in this research that your daughter has agreed to disclose or make available. For example, if your daughter requests in writing that information about your daughter or your daughter's participation in the research be released to an insurance company, the investigator may not use the Certificate of Confidentiality to withhold this information. This means that your daughter and your family should actively protect your daughter's own privacy. Finally, the investigator is not prevented from disclosing, including reporting to appropriate authorities, information concerning abuse, neglect or harm to others or yourself or your daughter.

For how long will the investigators be permitted to use and disclose identifiable information related to my daughter's participation in this research study?
The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your daughter's identifiable medical information) related to your daughter's participation in this research study for up to 5 years in order to complete this research study. As directed by University policy, all research records will be maintained for a period of at least 7 years following final reporting or publication of a project. Blood samples will be stored indefinitely.

May my daughter have access to my daughter's medical information that results from my daughter's participation in this research study?
In accordance with the HCWP Notices of Privacy Practices document that your daughter has been provided, your daughter is permitted access to information (including information and labs resulting from your daughter's participation in this research study) contained within your daughter's medical records filed with your daughter's health care provider unless otherwise specifically stated below.

Is my daughter's participation in this research study voluntary?
Your daughter's participation in this research study, to include the use and disclosure of your daughter's identifiable information for the purposes described above, is completely voluntary. (Note, however, that if your daughter does not provide your daughter's consent for the use and disclosure of your daughter's identifiable information for the purposes described above, your daughter will not be allowed, in general, to participate in the research study.) Whether or not your daughter provides your daughter's consent for participation in this research study will have no effect on your daughter's current or future relationship with the HCWP and the University of Pittsburgh. Whether or not your daughter provides your daughter's consent for participation in this research study will have no effect on your daughter's current or future medical care at HCWP or other health care provider or your daughter's current or future relationship with a health care insurer provider.

Your daughter's doctor is involved as an investigator in this research study. As both your daughter's doctor and a research investigator, she is interested both in your daughter's medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during your daughter's study participation, your daughter may discuss your daughter's care with another doctor who is not associated with this research study. Your daughter is not under any obligation to participate in any research study offered by your daughter's doctor.

May my daughter withdraw, at a future date, my daughter's consent for participation in this research study?
Your daughter may withdraw, at any time, your daughter's consent for participation in this research study, to include the use and disclosure of your daughter's identifiable information for the purposes described above. (Note, however, that if your daughter withdraws your daughter's consent for the use and disclosure of your daughter's identifiable information for the purposes described above, your daughter will also be withdrawn, in general, from further participation in this research study.) Any identifiable research or medical information recorded for, or resulting from, your daughter's participation in this research study prior to the date that your daughter formally withdrew your daughter's consent may continue to be used and disclosed by the investigators for the purposes described above. Your daughter may request to have your daughter's blood sample destroyed if your daughter withdraws from the study. To formally

withdraw your daughter's consent for participation in this research study, your daughter should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

Your daughter's decision to withdraw your daughter's consent for participation in this research study will have no effect on your daughter's current or future relationship with the HCWP and the University of Pittsburgh. Your daughter's decision to withdraw your daughter's consent for participation in this research study will have no effect on your daughter's current or future medical care at the HCWP or other health care provider or your daughter's current or future relationships with a health care insurance provider. If your daughter decides to withdraw from study participation after your daughter has received rVWF and/or TA, your daughter should participate in the described monitoring follow-up procedures directed at evaluating the safety of rVWF and/or TA. Your daughter has the right to request that your daughter's blood samples not already tested at the time your daughter withdraws be destroyed.

If my daughter agrees to take part in this research study, can my daughter be removed from the study without my daughter's consent?

It is possible that your daughter may be removed from the research study by the researchers. If your daughter's screening blood tests are out of range; if your daughter become pregnant; if your daughter is not compliant with taking study drug as directed; the study is incomplete; if your daughter receive other clotting medicine during the study; or if your daughter develop a side effect to rVWF and/or TA and it is not safe for your daughter to continue; your daughter may be withdrawn from participation in this study.

****

PARENTAL PERMISSION

All of the above has been explained to us, and our current questions have been answered. We understand that we are encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by the researchers listed on the first page of this form. Any questions which we may have about my daughter's rights as a research participant will be answered by the Human Subject Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668). A copy of this consent form will be given to us.

I understand that, as a minor (age less than 18 years), my daughter is not permitted to participate in this research study without my permission. Therefore, by signing this form, I give my permission for her participation in this research study, and authorize Dr. Ragni and their research team to access my daughter's medical records for the purposes described in this form.

_____
Parent's or Guardian's Name (Print)

_____ _____
Parent's or Guardian's Signature Date

ASSENT

This research has been explained to me, and I agree to participate.

_____
Printed Name of Daughter-Subject

_____ _____
Signature of Daughter-Subject Date

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions they had about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____ _____
Printed Name of Person Obtaining Consent Role in Research Study

_____ _____
Signature of Person Obtaining Consent Date

CONSENT FOR CONTINUED RESEARCH PARTICIPATION (For Subject Participants Reaching Age 18)

I understand that I am currently participating in a research study. I further understand that consent for my participation in this research study was initially obtained from my authorized representative as a result of my inability to provide direct consent at the time that this initial consent was requested. I have now turned age 18 and I am able to provide direct consent for continued participation in this research study.

The above information has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions, voice concerns or complaints about any aspect of this research study during the course of this study, and that such future questions, concerns or complaints will be answered by a qualified individual or by the investigator(s) listed on the first page of this consent document at the telephone number(s) given.

I understand that I may always request that my questions, concerns or complaints be addressed by a listed investigator. I understand that I may contact the Human Subjects Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668) to discuss problems, concerns, and questions; obtain information; offer input; or discuss situations in the event that the research team is unavailable. By signing this form I agree to participate in this research study.

By signing below, I agree to continue my participation in this research study. A copy of this consent form will be given to me.

_____ _____

Participant's Signature Date

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no research component of this protocol was begun until after this consent form was signed.

_____ _____

Name of Person Obtaining Consent (Print) Role in Research Study

_____ _____

Signature of Person Obtaining Consent Date

Appendix: Study Schedule

Table 1: Schedule of Events

Schedule of Events								
Study Week	**Week 0-4**	**Week 5-8**	**Week 9-12**	**Week 13-16**	**Week 17**	**Week 17-20**	**Week 21-24**	**Week 24**
Study Visit*	**Visit 1**	**Visit 2**			**Visit 3**			**Visit 4**
Cycle	**Screen**	**Pre-C1**	**Cycle 1**	**Cycle 2**	**Pre-C3**	**Cycle 3**	**Cycle 4**	**End**
Screening, Consent	X							
Baseline Clinical Assessment								
Medical History	X							X
Vital Signs	X							X
Physical Exam	X							
Concomitant Medications	X				X			X
Randomization, Enrollment		X						
End of Study								X
Baseline Laboratory								
Blood Count Tests: hemoglobin, platelets	X							
Iron Tests: Fe, TIBC, Ferritin	X							
Thyroid Test: TSH	X							
VWD Test: VWF:RCo, VWF:Ag, VIII, multimer, genotype	X							
Urine Pregnancy Test	X		X	X		X	X	
Primary Endpoint Measure								
Pictorial Blood Assessment Chart (PBAC)	X X		X	X		X	X	
Secondary Endpoint Measures								
Subject Diary: Cycle Severity Score, Duration,			X	X		X	X	
Quality of Life: SF-36, Ruta, CDCHRQoL-14, CES-D	X				X			X
Satisfaction Survey, Cost-Effectiveness Questionnaire					X			X
Adverse Events Assessment								
Allergic reaction			X	X	X	X	X	X
Thrombosis			X	X	X	X	X	X
Bleeding (other)			X	X	X	X	X	X

*Study Visit 1 is Baseline/Screen; Visit 2 is Pre-Cycle 1; Visit 3 is Pre-Cycle 3; and Visit 4 is Post-Cycle 4/ End. Cycles are consecutive months.

University of Pittsburgh

CONSENT TO ACT AS A SUBJECT IN A RESEARCH STUDY

TITLE: Prospective, Randomized, Crossover Trial Comparing Recombinant von Willebrand Factor (rVWF) vs. Tranexamic Acid (TA) to Minimize Menorrhagia in Women with von Willebrand Disease: The VWD Minimize Study

VERSION: 4.0 / 11 Dec 2019

PRINCIPAL INVESTIGATOR: Margaret V. Ragni, M.D., M.P.H.
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SOURCE OF SUPPORT: National Heart, Lung, Blood Institute,
National Institutes of Health

Why is this research being done?

The purpose of this research study is to compare the use of recombinant von Willebrand factor (rVWF) and tranexamic acid (TA, Lysteda®) in women with von Willebrand Disease (VWD) who have heavy monthly periods (also called menorrhagia). Von Willebrand disease is a common bleeding disorder genetic trait passed on in families (or inherited) that occurs in 1% of the population. It is caused by deficient or defective von Willebrand factor (VWF). Most people with VWD are treated with DDAVP (desmopressin), which is a protein given by vein or as an intranasal spray to treat bleeding symptoms. The problem is that some patients do not respond to DDAVP, or the response may be limited. This is because after three days, the stores of VWF become low (or depleted). Tranexamic acid is another treatment for menorrhagia, but it is less effective than DDAVP. Thus better treatments are needed for individuals with VWD.

In two clinical trials, rVWF has been shown to be safe and effective in treating and preventing bleeds in patients with VWD. Among women with menorrhagia in those trials, it also reduced menstrual bleeding. rVWF is approved by the U.S. Food and Drug Administration (FDA) for the treatment and prevention of bleeding, including menorrhagia (heavy monthly periods), in people with von Willebrand disease (VWD).

In the studies above, rVWF was given by intravenous (in a vein) infusion, reduced bleeding, and was safe and well-tolerated. In a survey of 16 hemophilia treatment centers, VWF concentrate has been used for menorrhagia only after first and second line treatments fail: in all 13 subjects receiving VWF there was reduction in heavy menstrual bleeding. In six published studies of rVWF or plasma-derived (pd) VWF concentrate, including two prospective, two retrospective and two observational studies of 455 VWD subjects, a total of 88 women received VWF 36-50 IU/kg for 1-6 days with reduction in menstrual bleeding in all women, and no adverse effects. Tranexamic acid (Lysteda®) in this study is taken as a pill by mouth three times daily. It is approved by the FDA for the treatment of menorrhagia.

Who is being asked to participate in this research study?
You are being asked to participate in this research study because you are a woman 13 to 45 years of age with VWD and you have heavy periods. You cannot participate if you are pregnant or lactating or if you are not willing to use a "double-barrier" method of contraception during the study. You must also be willing to avoid aspirin and nonsteroidal anti-inflammatory drugs, e.g. ibuprofen, during study. This site is one of approximately 25 sites in the United States and hopes to screen 20 subjects in order to enroll a total of 17-19 subjects (66 total subjects for the entire study). Your participation will last approximately 24 weeks (6 months). The projected duration of the study at all sites is expected to be around 5 years.

What procedures will be performed for research purposes?
If you decide to participate in this study, you will sign a consent form. This is a 24-week outpatient study that involves 4 visits. There are 3 parts to the study: pre-treatment, treatment, and post-treatment (described in detail below and in an appendix chart located end of this consent form). The study involves two treatment arms, Arms A and B, in which you will receive two drugs, one given by intravenous injection and one given orally. This study is called a "prospective randomized, crossover study" which means you will receive both treatment arms, but neither you nor your study doctor (or staff) will choose the order of the treatment arms.

If you agree to participate, you will be randomized (like a toss of a coin) to be in Group I or Group II for the first 5 days of menstrual bleeding in your next four consecutive menstrual cycles. There is an even (50/50) chance that you will be assigned first to either Group I or Group II treatment, as described here. If you are in **Group I**, you will receive **Arm A** for menstrual bleeding in cycles 1 and 2, followed by **Arm B** for menstrual bleeding in cycles 3 and 4. If you are in **Group II**, you will receive **Arm B** for menstrual bleeding in cycles 1 and 2, followed by **Arm A** for menstrual bleeding in cycles 3 and 4 (See Table below).

Group	**Cycles 1, 2**	**Cycles 3, 4**
Group I	**Arm A**: rVWF 40 IU/kg day 1	**Arm B**: TA 1300 mg po tid days 1-5
Group II	**Arm B**: TA 1300 mg po tid days 1-5	**Arm A**: rVWF 40 IU/kg day 1

rVWF is von Willebrand factor concentrate; TA is tranexamic acid; tid is three times daily; po is orally.

If you are in **Group I**, you will receive Arm A first: rVWF 40 IU/kg by intravenous injection on day 1 of menstrual bleeding in each of your next two menstrual cycles, "cycles 1 and 2." Then, you will crossover (switch) to receive Arm B: TA by mouth (2 pills which equal 1,300 mg) three times daily (tid) on days 1-5 during the first 5 days of menstrual bleeding in each of your next two menstrual cycles "cycles 3 and 4."

If you are in **Group II**, you will receive Arm B first: TA by mouth (2 pills which equal 1,300 mg) three times daily (tid) on days 1-5 during the first 5 days of menstrual bleeding in each of your next two menstrual cycles "cycles 1 and 2." Then you will crossover (switch) to receive Arm A: rVWF 40 IU/kg by intravenous injection on day 1 of menstrual bleeding in each of your next two menstrual cycles, "cycles 3 and 4."

Before you start the study drugs, you will have a brief medical history and physical exam and blood tests to check for thyroid function and iron deficiency. The HCWP nurses will also train you to give the rVWF infusion, but if you prefer a visiting nurse (OPTION CARE) to give rVWF in

your home, that can be arranged. During your next 4 monthly menstrual cycles (periods) you will receive rVWF alone for two cycles **AND** TA alone for two cycles, the order of which will be decided by randomization. These drugs can be taken in your home, or you can come into the center for the rVWF infusion.

There will be a total of 4 visits for outpatient monitoring by the Hemophilia Center of Western PA (HCWP). The drugs used in this study will be supplied by an NIH-contracted pharmacy, and shipped to the Hemophilia Center of Western PA. Your study drugs will be provided in a special kit for each cycle, which will be reviewed with the study nurse so you are completely familiar with the contents and how and when to take the study drug each cycle. The nurse will also provide you with a supply of tampons and pads, which you will use exclusively (no other tampons or pads will be permitted) during the study.

Study Visit 1: Screening Procedures, Week 0
To determine if you are eligible to take part in this study, you will have the following procedures performed:

- Review of informed consent: Dr. Ragni will review this document and answer any of your questions. If you decide to participate in the study, you will be asked to sign this informed consent document. A copy will be given to you for your records.
- Demographics and medical history: Your age, bleeding history, surgical history, any prescription and non-prescription drugs you are taking, and review of medical problems
- Physical examination and vitals will be taken: Including height, weight, blood pressure, respirations, temperature, pulse
- You will also be asked about the bleeding severity during your last 2 menstrual cycles.
- You will be asked to fill out 4 Quality-of-Life questionnaires (answering questions about how you are feeling, your daily activities, and bleeding).
- Urine pregnancy test
- Blood Draw: You will have ~1¾ tablespoon (~28 ml) of blood drawn for the following tests:
    - Blood Counts: hemoglobin, platelet count
    - Iron Tests: Iron, total iron blinding capacity (TIBC), and ferritin.
    - Thyroid Test: Thyroid stimulating hormone (TSH) to test thyroid function.
    - Von Willebrand Tests: von Willebrand factor (VWF) tests and genotype.

Dr. Ragni and her staff will review your past clinical and laboratory records to verify you have von Willebrand disease, which will be documented for research purposes. This one time visit will take about 2 hours. The Blood Count Tests, Iron Tests and Thyroid Test will be run by Quest Diagnostics in Pittsburgh, Pennsylvania. The von Willebrand Tests will be performed at the Francis Owen Blood Research Laboratory, in Chapel Hill, North Carolina, and genotype will be run at Functional Bioscience, Madison WI.

Study Visit 2: Before Menstrual Cycle 1, Week 4
The study nurse will contact you within a few days of screening to let you know if you are eligible or not. If you are not eligible, this will end your participation and you will not go on to receive study drug. If it is determined you are eligible to participate, you will be randomized to either Study Group I or Study Group II. All visits will be at the Hemophilia Center of Western Pennsylvania. The study nurse will also schedule your next appointment for you within the next few weeks.

> **Group I:** You will start with **Arm A:** You will take rVWF on day 1 of the next two monthly menstrual cycles (Cycles 1 and 2). This will be followed by **Arm B**: You will take TA for the first 5 days during the next two monthly menstrual cycles (Cycles 3 and 4).
>
> **Group II:** You will start with **Arm B:** You will take TA for the first 5 days during the next two monthly menstrual cycles (Cycles 1 and 2). This will be followed by **Arm A:** You will take rVWF on day 1 of the next two monthly menstrual cycles (Cycles 3 and 4).

At home, on day 1 of each of your next four menstrual cycles, you will perform a home pregnancy test (to make sure you are not pregnant). If the test indicates you are not pregnant, you may begin taking your study drug, either rVWF alone or TA alone. If you are not able to come to clinic or set up an OPTION CARE visit to administer rVWF on day 1 of the cycle to which you are assigned, you should notify your nurse, and plan to come in to HCWP or schedule OPTION CARE on Day 2. If your bleeding is not relieved after one dose of rVWF, your HTC doctor may give an additional dose of rVWF on the following day.

If you are assigned to rVWF, it is preferable that you take it in the morning, if possible. When you take TA, it is preferable that you take the first of your TA pills by mouth around 8:00 AM (at breakfast). You may take your second TA dose with lunch and third TA dose with dinner.

You will take rVWF for 1 day and TA for 5 days. You will record the pregnancy test results, menstrual bleeding and symptoms, and when you took the study drug in a diary, and how much you are bleeding in the Pictorial Blood Assessment Chart (PBAC) during each cycle. The diary can be accessed on any computer device (i.e., home computer, tablet computer, etc.) via a secure Internet connection. The HTC staff will train you on how to complete the diary entries and the PBAC score. If you do not have a personal computer, you can complete paper diaries and PBAC entries. You should call the study nurse coordinator to arrange your next visit and address any questions you may have. If at any time during this study, there are changes in your health or need to take any type new medication, you should call someone on the study team.

- You will be given a supply of study drugs to take during bleeding on your next 4 menstrual cycles, including Cycles 1, 2 (either rVWF alone **OR** TA alone) and Cycles 3, 4 (either TA alone OR rVWF alone).

- Your study nurse coordinator will review how and when you will administer study drug. If you choose to use a visiting nurse for rVWF infusion, this will be set up for you.

- You will be given access to complete the diary computer forms, or the paper copies will be provided for the diary and PBAC chart; and you will be given home urine pregnancy tests. You will review their use with the study nurse coordinator. The urine pregnancy test will be done at the onset of menses each cycle (cycle 1, 2, 3, 4) *before* you take the study drugs.

You will have 2 additional visits at the Hemophilia Center of Western PA. Dr. Ragni and study nurse will meet you there. The purpose of these visits is to (1) review the study drug (2) test your quality of life, and (3) review your menstrual bleeding severity using the PBAC chart. Each of these visits will last approximately 1 hour.

Study Visit 3: Before Menstrual Cycle 3, Week 16
At home, on day 1 of each of your next menstrual cycles, you will perform a home pregnancy test (to make sure you are not pregnant). If the test indicates you are not pregnant, you may begin taking your study drug, either rVWF alone or TA alone. If you are not able to come to clinic or set up an OPTION CARE visit to administer take rVWF on day 1 of the cycle to which you are assigned, you should notify your nurse, and plan to come in to HCWP or schedule OPTION CARE on Day 2. If your bleeding is not relieved after one dose of rVWF, your HTC doctor may give an additional dose of rVWF on the following day.

If you are assigned to rVWF, it is preferable that you take it in the morning, if possible. When you take TA, it is preferable that you take the first of your TA pills by mouth around 8:00 AM (at breakfast). You may take your second TA dose with lunch and third TA dose with dinner.

You will continue your assigned drug(s) as directed. You will complete the PBAC and diary, either via computer access or in paper format. You should call the study nurse coordinator to arrange your next visit and address any questions you may have. If at any time during this study, there are changes in your health or need to take any type new medication, you should call someone on the study team.

- You will review the study drugs to take during bleeding on your next 2 menstrual cycles, Cycles 3, 4 (either rVWF alone **OR** TA alone).

- Your study nurse coordinator will review how and when you will administer study drug. If you choose to use a visiting nurse for rVWF infusion, this will be set up for you.

- You will review your diary entries, urine pregnancy tests, and PBAC chart with the study nurse coordinator. The urine pregnancy test will be done at the onset of menses for each cycle *before* you take the study drugs.

- You will be asked to fill out 4 Quality-of-Life questionnaires (answering questions about how you are feeling, your daily activities, and bleeding), a satisfaction survey, and a cost-effectiveness questionnaire.

Study Visit 4: After Menstrual Cycle 4, End-Study Visit, Week 24
The final visit will be at the Hemophilia Center of Western PA. This visit will last approximately 1 hour where you will have the following procedures performed:

- Vital signs.

- You will be asked how you have been doing since your last visit (including any problems and any medications you are taking).

- A medical history will be performed by the physician or study nurse.

- Your diary entries, urine pregnancy test results, PBAC chart, and cycle severity score will be reviewed by the study nurse coordinator.

- Quality-of-Life questionnaires, a satisfaction survey, and a cost-effectiveness questionnaire will be completed.

- Unused study drugs will be collected.

This will complete your study participation.

Total Blood Draw

The total blood draw during this 24-week study is approximately 1¾ tablespoon (or 28 ml).

Blood Sample and Data Storage

As part of this study, we are obtaining data and blood samples from you. We would like to use this data and blood for this study. Your samples will be labeled with code numbers, and information linking the code numbers to your identity will be kept in a separate, locked file at the Hemophilia Center. Your von Willebrand Test blood samples will be stored indefinitely at the Francis Owen Blood Research Laboratory, University of North Carolina, and under the control of Dr. Nichols and Dr. Ragni. Dr. Nichols is engaged in von Willebrand Disease research. There is no plan at this time to share your data and samples outside of this study. Any request to share your data and samples with other researchers outside of this study must be approved in a formal application process with the NIH. Your samples will most likely be used up in the von Willebrand factor (VWF) and genotype testing, but leftover samples will be stored indefinitely unless you do not wish to have your samples stored.

If future testing is approved by the NIH for other research studies, this may provide additional information that will be helpful in understanding von Willebrand disease or other diseases or conditions, including research to develop investigational tests, treatments, drugs or devices that are not yet approved by the U.S. Food and Drug Administration. It is unlikely that what we learn from these studies will have a direct benefit to you. There are no plans to provide financial compensation to you should this occur. By allowing us to use your data and blood you give up any property rights you may have in the data and blood samples.

We will only share your data and blood samples with other researchers if the NIH approves this action via the formal application process described above. They may be doing research in areas similar to this research or in other unrelated areas. These researchers may be at the University of Pittsburgh, at other research centers and institutions, or industry sponsors of research. We may also share your research data with large data repositories (a repository is a database of information) for broad sharing with the research community. If your individual research data is placed in one of these repositories only qualified researchers, who have received prior approval from individuals that monitor the use of the data, will be able to look at your information.

If you change your mind and do not want us to store and use your data and blood samples for future research you should contact the research team member identified at the top of this document. The data and blood samples will no longer be used for research purposes. However, if some research with your data and blood samples has already been completed, the information from that research may still be used. Also, if the data and blood has been shared with other researchers it might not be possible to withdraw the data and blood to the extent it has been shared.

What are the possible risks, side effects, and discomforts of this research study?
As with any investigational study, there may be adverse events or side effects that are currently unknown and it is possible that certain of these unknown risks could be permanent, serious, or life-threatening. There may be risks and discomforts associated with these products and study treatment that are not yet known at this time. Should you encounter any side effects you think might be related to this study or the drugs, you should contact Dr. Ragni immediately.

Risk of Blood Drawing
There may be discomfort with drawing blood, which is common, and may include pain, lightheadedness bruising, or bleeding or infection in the tissue around the vein. This may be alleviated or reduced by applying pressure to the blood draw site for 5 minutes, and by lying on your back with your head flat and knees bent if you feel lightheaded. The risk of repeated blood draws is anemia, or a low blood count, but this will be carefully monitored. Injections may rarely cause pain, soreness, redness, warmth, itching, numbness, tenderness, swelling, skin changes (discoloration, breakdown, or thickening), or swelling or lymph nodes near the injection site.

Risk of Inadvertent Disclosure
There is a possibility that if the result of the research studies involving your medical record or genetic material were to become generally known, this information could impact future insurability, employability, or reproduction plans, or have a negative impact on family relationships, and/or result in paternity suits or stigmatization (identifying as unusual, different).

Risk of Allergic Reaction
An allergic reaction to study treatment with rVWF may rarely occur, in less than 0.001% or 1 in 100,000 people, and could cause in decreasing order of severity: death, anaphylaxis, which is a life-threatening reaction causing difficulty breathing, low blood pressure and irregularity of the heartbeat, hypervolemia (overabundance of body fluid), paresthesias (prickling sensation), urticaria (hives) generalized or localized to the injection site, chest tightness, rash, pruritus (itching), and/or edema (swelling), fever, and chills. The dose chosen for the study, 40 IU/kg, appears to be safe and well tolerated in clinical trials.

An allergic reaction to treatment with TA is rare. Symptoms may include chills, fever, nausea and vomiting, or rarely may include in decreasing order of severity: death, anaphylaxis, which is a life-threatening reaction causing difficulty breathing, low blood pressure, heart irregularity, increase in body fluids, paresthesias (numbness or pricking sensation), urticaria (hives), chest tightness, rash, pruritus (itching), edema (swelling), fever, and/or chills. Should this occur, Benadryl, a medication which reduces inflammation, may be given, with close monitoring of these symptoms. Benadryl may cause drowsiness, dizziness or low blood pressure. You will be monitored for these symptoms while receiving drugs.

No one with a known allergy to either rVWF or TA will be enrolled in this study.

Risk of Thromboembolism
Although rVWF and TA increase blood protein levels, there is the rare possibility that rVWF or TA could cause a clot in the vein (thrombosis) with swelling, pain, or a clot in the lung (pulmonary embolus) with shortness of breath or coughing up blood. This risk will be very carefully monitored clinically. The use of oral contraceptives with TA may increase risk of venous thromboembolism, and thus will not be allowed during study. Should these symptoms occur; measures considered standard of care would be implemented to prevent clots: these include either compression stockings, which are support-like stockings, and/or sequential

compression devices (SCDs). SCDs are blanket-like Velcro-devices which are placed on the legs to promote blood flow and prevent clots from forming in the leg veins. Treatment, should a clot occur, would primarily consist of stopping the study product as soon as possible. If needed, the risks and benefits of anticoagulation will be considered.

Risk of Bleeding Events
Bleeding symptoms may occur in VWD unrelated to this study, usually with trauma, but sometimes spontaneously, without cause. Although unlikely, if you have bleeding, or if you have menstrual bleeding not controlled after five days with study drugs, standard treatment, DDAVP or factor concentrate whichever you usually use, will be given.

Risk of Pregnancy
rVWF has not been studied in pregnant women. Thus, it is recommended that pregnancy should be avoided in subjects on this study. Avoiding sexual activity is the only certain method to prevent pregnancy. However, if you choose to be sexually active, you must agree to use an appropriate double barrier method of birth control, such as female use of a diaphragm, non-hormonal intrauterine device (IUD), sponge and spermicide, in addition to the male use of a condom. The double barrier contraception must be used for at least one week prior to the start of the research study and continue for at least two weeks following the last study visit. If you choose to be sexually active during this study, you must accept the risk that pregnancy could still result, exposing you and your sexual partner to potential loss of pregnancy as well as other unknown effects on the developing fetus.

Birth Control Statement
If you become aware that you are pregnant or become pregnant during the course of this research study, you must contact the principal investigator and physician immediately. The effects of rVWF on the fetus (unborn child) are not fully known. It is therefore important that you do not become pregnant during this research study. You should not use hormones or a birth control implant during this study because of thrombosis (clot) risk. Double barrier contraception must be used for at least one week prior to the start of the research study and continue for at least two weeks following the last study visit.

Breach of confidentiality
There is also a potential for possible risk of breach of confidentiality of collected information. To minimize this risk, your study participation and related information will be protected to maintain confidentiality. Your blood samples and clinical history will be assigned an alphanumeric identifier and the key for linking this number with your identity will be kept at HCWP under lock and key by Dr. Ragni and her research staff. The de-identified information in this study will be placed into a secure, web-based data base at University of Pittsburgh Center for Research in Health Care Data Center (CRHC DC). If the investigator publishes research information, your name will not be identified.

A description of this clinical trial will be available on http://www.clinicaltrials.gov, as required by US Law. This website will not include information that can identify you. At most, the website will include a summary of the results. You can search this website at any time.

What are the possible benefits from taking part in this study?
It is possible that rVWF and/or TA will reduce your heavy menstrual bleeding. However, there is no guarantee that you will receive such a benefit. If the information gathered from the use of rVWF and/or TA during menstrual periods, including reducing bleeding and increasing von Willebrand tests (VWF and related factors), then this may provide important information for the future use of rVWF

and/or TA for bleeding in individuals with VWD, when standard therapy is inadequate.

What treatments or procedures are available if I decide not to take part in this research study?
If you choose not to participate in this study, you understand that you will receive the usual medical care appropriate for your condition. You will receive DDAVP or available VWF clotting factor if you were to have bleeding or surgery or procedures. TA (Lysteda®) is commonly prescribed for women without VWD for menorrhagia.

If I agree to take part in this research study, will I be told of any new risks that may be found during the course of the study?
If new information becomes available during your participation in this study that may influence your willingness to participate, your doctor will communicate this to you promptly.

Will my insurance provider or I be charged for the costs of any procedures performed as part of this research study?
All procedures associated with this study are for research, including laboratory tests, out-patient hospitalization, study drugs, drug injections, and blood sampling. Neither you nor your insurer will be billed for any research-only services. The study drugs have been provided by pharmaceuticals that manufacture the drugs and their distribution will be covered by a grant from the National Institutes of Health to the University of Pittsburgh and Dr. Ragni. You will be responsible for any routine medical care not part of this experimental study, should such costs arise. The cost of DDAVP or clotting factor, should they be needed, is considered standard of care, and you or your third-party payer will be responsible for associated costs. You will be responsible for any applicable co-pays, coinsurances and deductibles.

Will I be paid if I take part in this research study?
You will be compensated $100.00 for each visit, for a total of $400.00 if you complete all parts of this study. If, for whatever reason, you complete part but not all of the study, the terms of this payment will be $100 for completing the initial Screening (visit 1); and $100 per visit for the 3 study visits 2-4. You will not be compensated for any additional visits. You will be paid only after you complete all visits for the study. Please allow 4-6 weeks.

You will be paid on a reloadable debit card. All compensation is taxable income to the participant regardless of the amount. If you receive $600 or more in a calendar year from one organization, that organization is required by law to file a Form 1099 – Miscellaneous with the IRS and provide a copy to the taxpayer. Individuals who do not provide a social security number may still participate in the research, but the IRS requires that 28% of the payment be sent by the institution to the IRS for 'backup withholding;' thus you would only receive 72% of the expected payment.

Who will pay if I am injured as a result of taking part in this study?
If you believe that you are injured as a result of the research procedures being performed, please contact immediately the Principal Investigator listed on the first page of this form. Emergency medical treatment for injuries solely and directly related to your participation in this research study will be provided to you by the hospitals of the UPMC. It is possible that UPMC may bill your insurance provider for the costs of this emergency treatment, but none of these costs will be charged directly to you. If your research-related injury requires medical care beyond this emergency treatment, you will be responsible for the costs of this follow-up care unless otherwise specifically stated below. There is no plan for monetary compensation. You do not, however, waive any legal rights by signing this form.

Will this research study involve the use or disclosure of my identifiable medical information?
This research study will involve the recording of current and/or future identifiable medical information from your hospital and/or other (e.g. physician office) records. The information that will be recorded will be limited to information concerning Blood Counts, Iron Tests, Thyroid Test, and von Willebrand tests you are scheduled to undergo, the results of these tests, and any adverse events associated with testing. This information will be used for the purpose of determining individuals in whom rVWF and TA are effective and for potential treatment for menorrhagia.

This research study will result in identifiable information that will be placed into your medical records held at the Hemophilia Center. The nature of the identifiable information resulting from your participation in the research study that will be recorded in your medical record includes the results of the Blood Counts, Iron Tests, Thyroid Test, and von Willebrand Tests, along with any information related to any adverse events you may suffer during these tests.

Who will have access to identifiable information related to my participation in this research study?
In addition to the investigators listed on the first page of this authorization (consent) form and their research staff, the following individuals will or may have access to identifiable medical information related to your participation in this research study. Authorized representatives of the University of Pittsburgh Office of Research Protections may review your identifiable research information (which may include your identifiable medical information) for the purpose of monitoring the appropriate conduct of this research study.

In unusual cases, the investigators may be required to release identifiable information (which may include your identifiable medical information) related to your participation in this research study in response to an order from a court of law. If the investigators learn that you or someone with whom you are involved is in serious danger or potential harm, they will need to inform, as required by Pennsylvania law, the appropriate agencies.

Authorized representatives will review and/or obtain identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purposes of monitoring the accuracy and completeness of the research data and for performing required scientific analyses of the research data. Your blood samples will be stored indefinitely at the Francis Owen Blood Research Laboratory, University of North Carolina, and under the control of Dr. Nichols and Dr. Ragni. There is no plan for the samples to undergo other tests or be given to other investigators. If such a plan were considered, you would be re-consented for your approval. No additional samples will be required than those in the current study. While the study sponsor understands the importance of maintaining the confidentiality of your identifiable research and medical information, the University of Pittsburgh cannot guarantee the confidentiality of this information after it has been obtained by others.

Authorized representatives of the National Institutes of Health, U.S. Food and Drug Administration may review and/or obtain identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of monitoring the accuracy of the research data.

While the external agencies mentioned understand the importance of maintaining the

confidentiality of your identifiable research and medical information, the University of Pittsburgh and HCWP cannot guarantee the confidentiality of this information after it has been obtained by the any external monitoring entity.

Authorized representatives of HCWP and other health care providers may have access to identifiable information (which may include your identifiable medical information) related to your participation in this research study for the purpose of (1) fulfilling orders, made by the investigators, for hospitals and health care services (e.g. laboratory tests, diagnostic procedures associated with research study participation; (2) addressing correct payment for tests and procedures ordered by the investigators; and/or (3) for internal hospital operations (i.e. quality assurance).

To further protect your privacy, the investigator has obtained a Certificate of Confidentiality from the federal government. This Certificate may prevent the investigator from being forced (for example by court subpoena) to disclose information that may identify you in any federal, state, or local civil, criminal, administrative, legislative, or other proceeding. However, a Certificate of Confidentiality does not prohibit the investigator from disclosing information about you or your involvement in this research that you have agreed to disclose or make available. For example, if you request in writing that information about you or your participation in the research be released to an insurance company, the investigator may not use the Certificate of Confidentiality to withhold this information. This means that you and your family should actively protect your own privacy. Finally, the investigator is not prevented from disclosing, including reporting to appropriate authorities, information concerning abuse, neglect or harm to others or yourself.

For how long will the investigators be permitted to use and disclose identifiable information related to my participation in this research study?

The investigators may continue to use and disclose, for the purposes described above, identifiable information (which may include your identifiable medical information) related to your participation in this research study for up to 5 years in order to complete this research study. As directed by University policy, all research records will be maintained for a period of at least 7 years following final reporting or publication of a project. Blood samples will be stored indefinitely.

May I have access to my medical information that results from my participation in this research study?

In accordance with the HCWP Notices of Privacy Practices document that you have been provided, you are permitted access to information (including information and labs resulting from your participation in this research study) contained within your medical records filed with your health care provider unless otherwise specifically stated below.

Is my participation in this research study voluntary?

Your participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above, is completely voluntary. (Note, however, that if you do not provide your consent for the use and disclosure of your identifiable information for the purposes described above, you will not be allowed, in general, to participate in the research study.) Whether or not you provide your consent for participation in this research study will have no effect on your current or future relationship with the HCWP and the University of Pittsburgh. Whether or not you provide your consent for participation in this research study will have no effect on your current or future medical care at HCWP or other health care provider or your current or future relationship with a health care insurer provider.

Your doctor is involved as an investigator in this research study. As both your doctor and a research investigator, she is interested both in your medical care and the conduct of this research study. Before agreeing to participate in this research study, or at any time during your study participation, you may discuss your care with another doctor who is not associated with this research study. You are not under any obligation to participate in any research study offered by your doctor.

May I withdraw, at a future date, my consent for participation in this research study?

You may withdraw, at any time, your consent for participation in this research study, to include the use and disclosure of your identifiable information for the purposes described above. (Note, however, that if you withdraw your consent for the use and disclosure of your identifiable information for the purposes described above, you will also be withdrawn, in general, from further participation in this research study.) Any identifiable research or medical information recorded for, or resulting from, your participation in this research study prior to the date that you formally withdrew your consent may continue to be used and disclosed by the investigators for the purposes described above. You may request to have your blood sample destroyed if you withdraw from the study. To formally withdraw your consent for participation in this research study, you should provide a written and dated notice of this decision to the principal investigator of this research study at the address listed on the first page of this form.

Your decision to withdraw your consent for participation in this research study will have no effect on your current or future relationship with the HCWP and the University of Pittsburgh. Your decision to withdraw your consent for participation in this research study will have no effect on your current or future medical care at the HCWP or other health care provider or your current or future relationships with a health care insurance provider. If you decide to withdraw from study participation after you have received rVWF and/or TA, you should participate in the described monitoring follow-up procedures directed at evaluating the safety of rVWF and/or TA. You have the right to request that your blood samples not already tested at the time you withdraw be destroyed.

If I agree to take part in this research study, can I be removed from the study without my consent?

It is possible that you may be removed from the research study by the researchers. If your screening blood tests are out of range; if you become pregnant; if you are not compliant with taking study drug as directed; the study is incomplete; if you receive other clotting medicine during the study; or if you develop a side effect to rVWF and/or TA and it is not safe for you to continue; you may be withdrawn from participation in this study.

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VOLUNTARY CONSENT

All of the above has been explained to me and all of my current questions have been answered. I understand that I am encouraged to ask questions about any aspect of this research study during the course of this study, and that such future questions will be answered by the researchers listed on the first page of this form. Any questions which I have about my rights as a research participant will be answered by the Human Subject Protection Advocate of the IRB Office, University of Pittsburgh (1-866-212-2668).

By signing this form, I consent to participate in this research study and provide my authorization to share my medical records with the research team. A copy of this consent form will be given to me.

_____
Printed Name of Participant

_____ _____
Participant's Signature Date and Time

CERTIFICATION of INFORMED CONSENT

I certify that I have explained the nature and purpose of this research study to the above-named individual(s), and I have discussed the potential benefits and possible risks of study participation. Any questions the individual(s) have about this study have been answered, and we will always be available to address future questions as they arise. I further certify that no component of this protocol was begun until after consent was signed.

_____ _____
Printed Name of Person Obtaining Consent Role in Research Study

_____ _____
Signature of Person Obtaining Consent Date and Time

Appendix: Study Schedule

Table 1: Schedule of Events

Schedule of Events								
Study Week	**Week 0-4**	**Week 5-8**	**Week 9-12**	**Week 13-16**	**Week 17**	**Week 17-20**	**Week 21-24**	**Week 24**
Study Visit*	**Visit 1**	**Visit 2**			**Visit 3**			**Visit 4**
Cycle	**Screen**	**Pre-C1**	**Cycle 1**	**Cycle 2**	**Pre-C3**	**Cycle 3**	**Cycle 4**	**End**
Screening, Consent	X							
Baseline Clinical Assessment								
Medical History	X							X
Vital Signs	X							X
Physical Exam	X							
Concomitant Medications	X				X			X
Randomization, Enrollment		X						
End of Study								X
Baseline Laboratory								
Blood Count Tests: hemoglobin, platelets	X							
Iron Tests: Fe, TIBC, Ferritin	X							
Thyroid Test: TSH	X							
VWD Test: VWF:RCo, VWF:Ag, VIII, multimer, genotype	X							
Urine Pregnancy Test	X		X	X		X	X	
Primary Endpoint Measure								
Pictorial Blood Assessment Chart (PBAC)	X X		X	X		X	X	
Secondary Endpoint Measures								
Subject Diary: Cycle Severity Score, Duration,			X	X		X	X	
Quality of Life: SF-36, Ruta, CDCHRQoL-14, CES-D	X				X			X
Satisfaction Survey, Cost-Effectiveness Questionnaire					X			X
Adverse Events Assessment								
Allergic reaction			X	X	X	X	X	X
Thrombosis			X	X	X	X	X	X
Bleeding (other)			X	X	X	X	X	X

*Study Visit 1 is Baseline/Screen; Visit 2 is Pre-Cycle 1; Visit 3 is Pre-Cycle 3; and Visit 4 is Post-Cycle 4/ End. Cycles are consecutive months.