

## **APPENDIX:**

### **Recombinant von Willebrand Factor and Tranexamic Acid for Heavy Menstrual Bleeding in VWD: Randomized Crossover Trial**

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**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**



*Short Title:* **The VWDMin Trial**

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**Summary of Changes from Previous Version:**

<b>Affected Section(s)</b>	<b>Summary of Revisions Made</b>	<b>Rationale</b>
<b>Study Design, Study Population, Sections 2.3.1, 5.2</b>	Exclusion criteria revised to clarify use of hormones (other than progesterone-only), or combined oral contraceptives, and contraceptive implants in past 3 months.	While hormonal contraception has been a contraindication (when using lysteda, and because they increase VWF), progesterone alone contraception does not increase thrombotic risk nor is it a contraindication with Lysteda.

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## STATEMENT OF COMPLIANCE

The trial will be carried out in accordance with International Conference on Harmonisation Good Clinical Practice (ICH GCP) and the following:

- United States (US) Code of Federal Regulations (CFR) applicable to clinical studies (45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56, 21 CFR Part 312, and/or 21 CFR Part 812)

National Institutes of Health (NIH)-funded investigators and clinical trial site staff who are responsible for the conduct, management, or oversight of NIH-funded clinical trials have completed Human Subjects Protection and ICH GCP Training.

The protocol, informed consent form, recruitment materials, and all participant materials will be submitted to the Institutional Review Board (IRB) for review and approval. Approval of both the protocol and the consent form must be obtained before any participant is enrolled. Any amendment to the protocol will require review and approval by the IRB before the changes are implemented to the study. In addition, all changes to the consent form will be IRB-approved; a determination will be made regarding whether a new consent needs to be obtained from participants who provided consent, using a previously approved consent form.

### INVESTIGATOR AGREEMENT

I confirm agreement to conduct the study in compliance with the protocol.

I acknowledge that I am responsible for overall study conduct. I agree to personally conduct or supervise the described clinical study.

I agree to ensure that all associates, colleagues and employees assisting in the conduct of the study are informed about their obligations. Mechanisms are in place to ensure that site staff receives the appropriate information throughout the study.

Investigator Name:

\_\_\_\_\_

Site #:

\_\_\_\_\_

Investigator Signature:

\_\_\_\_\_

Date:

\_\_\_\_\_

## 1 PROTOCOL SUMMARY

### 1.1 SYNOPSIS

<b>Title:</b>	<b>The Von Willebrand Disease Minimize Menorrhagia (VWDMin) TRIAL</b>
<b>Study Description:</b>	This is a prospective, randomized, crossover multicenter clinical trial comparing recombinant von Willebrand factor (rVWF, Vonvendi) and tranexamic acid (TA, Lysteda) to reduce menorrhagia in women with von Willebrand disease. We <i>hypothesize</i> that intravenous rVWF given on day 1 of 2 consecutive menstrual cycles is more effective than oral TA three times daily on days 1-5 of 2 consecutive menstrual cycles in reducing menstrual blood loss and improving quality of life, despite its higher cost and invasive route of administration. A total of 60 women (inflated to 66 for anticipated 10% dropout) with VWD 13-45 years old will be enrolled 24 weeks each in this 5-year trial.
<b>Objectives:</b>	The <b>Primary Objective</b> is to determine the efficacy of rVWF vs. TA in reducing menorrhagia in women with VWD. The <b>Secondary Objective</b> is to evaluate safety, tolerability, acceptability of rVWF vs. TA in reducing menorrhagia in women with VWD.
<b>Endpoints:</b>	The <b>Primary Endpoint</b> is a 40-point reduction in pictorial blood assessment chart (PBAC) after 2 cycles. The <b>Secondary Endpoints</b> are cycle severity, cycle duration, and quality-of-life by SF-36, Ruta Menorrhagia Severity Scale, CDC-HRQoL-14, CES-D, and satisfaction survey. The cost-effectiveness questionnaire is exploratory.
<b>Study Population:</b>	Study subjects will be females age 13-45 years of age with von Willebrand disease, defined by VWF:RCo < 0.50 IU/ml (historic or current), previous bleeding history, who have menorrhagia and a PBAC >100 in at least one of the two preceding menstrual cycles, and cared for at one of the 25 or more U.S. centers (HTCs) participating in this trial. Sixty eligible subjects will be enrolled (inflated to 66 for anticipated 10% dropout).
<b>Phase:</b>	This is a phase III prospective, randomized, crossover trial.
<b>Description of Sites/Facilities</b>	Participating sites include approximately 25 U.S. hemophilia treatment centers (HTCs).
<b>Enrolling Participants:</b>	
<b>Description of Study Intervention:</b>	There are two study interventions: recombinant VWF and tranexamic acid. <u>Recombinant von Willebrand factor (rVWF, Vonvendi®)</u> is an FDA-approved clotting factor approved for treatment or prevention of bleeds including menorrhagia in VWD. It is an intravenous agent administered in single-use vials containing approximately 650-1300 IU mg per vial as a sterile, lyophilized powder. The vials are reconstituted with 5-10 ml vial of sterile water for injection, USP, which is transferred by two-way needle into the lyophilized powder for reconstitution, and the reconstituted vial infused slowly over 5-

10 minutes, at a dose of 40 mg/kg on the first day of menstrual bleeding in two cycles, with a single rescue dose allowed day 2.

Tranexamic acid (TA, Lysteda®) is an FDA-approved anti-fibrinolytic agent for treatment of menorrhagia in bleeding disorders. It is provided as two 650 mg tablets for a dose of 1300 mg three times daily for the first 5 days of menstrual bleeding in two cycles.

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 recombinant von Willebrand factor concentrate. TA is tranexamic acid; tid is three times daily.

**Study Duration:** This is a 24-week outpatient trial in which all subjects will be randomized to one of two treatment arms and followed for up to 24 weeks. Data analyses will be completed by 60 months from when the study opens to enrollment.

**Participant Duration:** The total time for each subject to complete all study visits is 6 months.

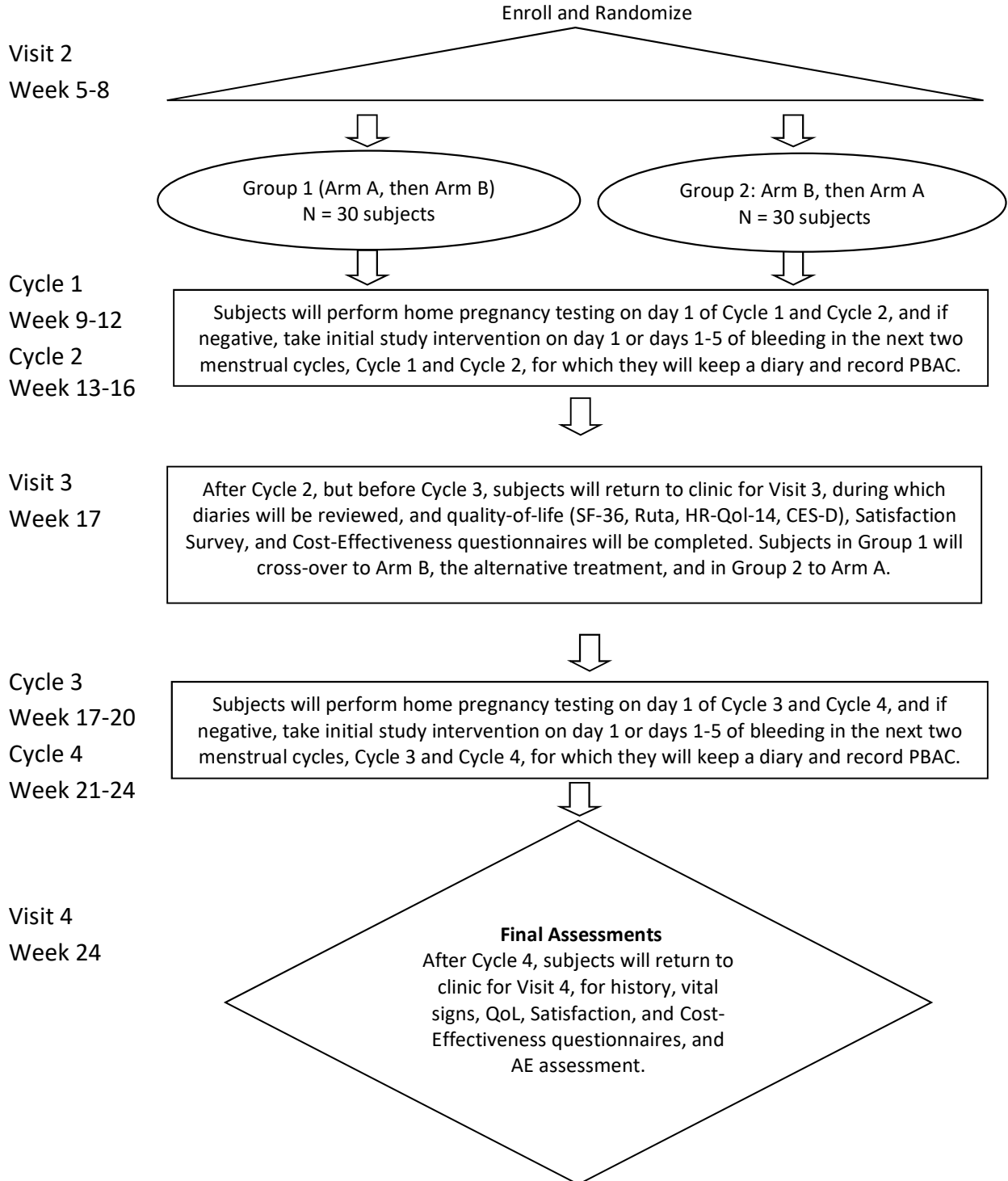
## 1.2 SCHEMA

### Visit 1

Screening: Obtain informed consent. Screen potential participants by inclusion and exclusion criteria; obtain history; physical exam; baseline labs, including hemoglobin, hematocrit, platelets, Fe, TIBC, ferritin, TSH, VWF assays (VWF:RCoF, VWF:Ag, FVIII, multimers), genotype), urine pregnancy test; PBAC score for the previous 2 cycles; and quality-of-life questionnaires, SF-36, Ruta, CDC HR-QoL-14, and CES-D.



Week 0-4



### 1.3 SCHEDULE OF ACTIVITIES (SOA)

The Schedule of Events is provided below.

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
<b>Screening, Consent</b>	X							
<b>Baseline Clinical Assessment</b>								
Medical History	X							X
Vital Signs	X							X
Physical Exam	X							
Concomitant Medications	X				X			X
<b>Randomization, Enrollment</b>		X						
<b>End of Study</b>								X
<b>Baseline Laboratory</b>								
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	
<b>Primary Endpoint Measure</b>								
Pictorial Blood Assessment Chart (PBAC)	X X		X	X		X	X	
<b>Secondary Endpoint Measures</b>								
Subject Diary: Cycle Severity Score, Duration, Quality of Life: SF-36, Ruta, CDCHRQoL-14, CES-D	X		X	X	X	X	X	X
Satisfaction Survey, Cost-Effectiveness Questionnaire					X			X
<b>Adverse Events Assessment</b>								
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/End. Cycles are consecutive months*

## 2 INTRODUCTION

### 2.1 STUDY RATIONALE

Ineffective therapies for menorrhagia is the greatest unmet healthcare need in women with bleeding disorders and menorrhagia, and there are few studies to guide future management this is a critical time to initiate a clinical trial of agents to treat menorrhagia in women with VWD. Given the high frequency of menorrhagia in women with von Willebrand disease (VWD), the associated morbidity including iron deficiency anemia with its social, cognitive, and mental consequences, and the lack of safe, effective therapies, it is critical to initiate a clinical trial of agents to treat menorrhagia in women with VWD. Although intravenous rVWF is more difficult to administer and costs more than oral tranexamic acid, the #1 current recommended non-hormonal treatment for menorrhagia, clinical studies of 101 women with VWD and menorrhagia indicate VWF, including both plasma-derived VWF and recombinant VWF, is effective in safely reducing menorrhagia in 95% or more (10, 11). Studies of TA indicate it reduced menorrhagia by 50% in up to 30% of women with bleeding disorders and menorrhagia (27, 41). With the prolonged half-life of rVWF, we anticipate that a single day of rVWF given day 1 of menstrual bleeding in the menstrual cycle will reduce menorrhagia to a greater degree than TA given on days 1-5 of the menstrual cycle. Given the gaps and unmet needs in the current care and management of menorrhagia in

women with VWD, it is a critical time to initiate a clinical trial to address the needs and improve the care of women with bleeding disorders. We, therefore, propose this Phase III multicenter prospective, randomized, crossover arm trial is to compare recombinant von Willebrand factor (rVWF, Vonvendi) to tranexamic acid (TA, Lysteda) in reducing the severity of menorrhagia in women with von Willebrand disease. The findings of this study will have potential impact on scientific, economic, and clinical aspect of care of women with VWD and menorrhagia. The findings will also provide data on new therapies for menorrhagia in women with VWD and other bleeding disorders, which, if successful, will improve clinical health outcomes and reduce days lost from work, lifestyle disruptions, psychological morbidity, health care cost, and poor quality of life. Further, as VWF is a risk factor for cardiovascular disease, determining the lowest effective VWF dose, acceptability of this intravenous therapy in women with VWD population will be critical in assuring no increase in thrombosis and cardiovascular disease. Finally, the goals of the study, i.e. to prevent complications and blood product safety, are consistent with the goals of Healthy People 2020 (40).

## 2.2 BACKGROUND

Von Willebrand disease (VWD) is the most common inherited bleeding disorder resulting from deficient or defective von Willebrand factor (VWF), and characterized by mucosal bleeding in the oropharyngeal, gastrointestinal, and genitourinary tract (1-3). Among women with VWD, up to 80% have menorrhagia (4, 5) which leads to significant morbidity, iron deficiency anemia, high health cost, and poor quality of life. Yet, the lack of effective therapy for menorrhagia is the greatest *unmet healthcare need* in women with VWD (5, 6). Up to 30% avoid DDAVP, hormones, or the recommended non-hormonal agent, tranexamic acid (TA), as they are ineffective or poorly tolerated (7), and few prospective trials are available to guide treatment.

Two recent trials of rVWF have been conducted: first, a phase I study to assess safety and pharmacokinetics of rVWF (8) and a Phase III study to assess efficacy in treatment and prevention of bleeding in VWD (9). In the latter, women with VWD and menorrhagia received rVWF which successfully reduced their menstrual bleeding. In these trials, rVWF was given by intravenous infusion, and safely and effectively reduced bleeding, and was well-tolerated. rVWF is licensed by the U.S. Food and Drug Administration (FDA) for the treatment and prevention of bleeding in VWD. In a survey of 16 hemophilia treatment centers, VWF concentrate has been used as a third-line treatment for menorrhagia, only after first- and second-line treatment failed: in all 13 subjects receiving VWF there was reduction in heavy menstrual bleeding (10, 11). In six published studies (9, 12-16), including two prospective trials, two retrospective trials, and two observational network studies, a total of 455 VWD subjects were treated with plasma-derived (pd) VWF or rVWF concentrate. Of these, one-third or 88 (19.2%) were women with type 1, 2, or 3 VWD and menorrhagia treated with pdVWF at a dose of 36-50 IU/kg for 1-6 days of menstrual cycle bleeding (10, 11). In these studies, 95-100% of these women reported reduction in menorrhagia, with no reported adverse effects. The purpose of this study is to compare whether rVWF is more effective than TA in reducing bleeding in women with menorrhagia. rVWF is invasive, requiring intravenous injection and costs more than oral TA: thus, to justify its use, rVWF should be more effective than TA alone. The use of rVWF in VWD is approved by the U.S. Food and Drug Administration (FDA) for

treatment of bleeding, including menorrhagia, in individuals with VWD. The formulation of tranexamic acid (TA, Lysteda®) in this study is in pill form. The pills are taken by mouth, three times daily. This drug and dose are currently licensed by the FDA for treatment of menorrhagia. It is critical and timely to address the problem of menorrhagia in women with VWD. We have accumulated data in our U34 feasibility study that women with VWD and physicians who care for them are willing to use an intravenous VWF to treat women with menorrhagia unresponsive to first and second line drugs, e.g. standard hormonal and non-hormonal therapy. It is critical to assess response of menorrhagia to rVWF vs. TA, as the findings will impact clinical management and improve health outcomes for women with VWD.

Von Willebrand disease (VWD) is the single most common congenital bleeding disorder, occurring in 1-3% of the population (1), and is characterized by deficiency or defect in von Willebrand factor (VWF), a glycoprotein that promotes platelet adhesion to vessel wall after vessel injury, which is crucial for platelet plug formation, or primary hemostasis, and serves as a carrier protein for factor VIII (2). The VWF gene is located on the short arm of chromosome 12 and is encoded by an 8.7 kb VWFmRNA expressed by vascular endothelial cells and bone marrow megakaryocytes (3). Typical bleeding symptoms include mucosal bleeding in the oropharyngeal, gastrointestinal, and genitourinary tract (1-3). Among women with VWD, the most common symptom is heavy menstrual bleeding, or menorrhagia, occurring in more as many as 80% (3-5).

Menorrhagia is associated with significant morbidity, including iron deficiency anemia up to two-thirds, early hysterectomy, and reduced quality of life (4-5, 17-19). Among women with menorrhagia, the prevalence of VWD is 5-20%, with overall prevalence of 13% (4-5, 20). These figures may underestimate the true prevalence of menorrhagia, as it may not be recognized as symptom of a coagulation disorder or not readily diagnosed, as the extragenic influences of blood group, exogenous estrogens, and stress, may increase VWF and lead to apparently normal VWF studies (2-3). Menorrhagia is defined as menstrual bleeding exceeding 80 cc/month, a level at which progressive iron loss and iron deficiency anemia occur (19). The health burden of menorrhagia is high, with excess days lost from work, lifestyle disruptions, psychologic morbidity, poor quality of life, and increased health care costs (17-18). It has been estimated that 5-10% of those in reproductive age seek medical attention (21), of whom 50% undergo surgical procedure (22). Only recently has consideration of underlying disorders of hemostasis been considered important in assessment of the woman with menorrhagia (5), and as a result women presenting with heavy menstrual bleeding are screened for bleeding disorders and other pathology prior to the procedure (23), resulting in a significant reduction from the nearly 50% of women undergoing hysterectomies for menorrhagia in the 1990s (17).

The “gold standard” for measuring menstrual blood loss by alkaline haematin spectrophotometry in collected pads and tampons, but as this is impractical, menstrual history is used in general practice (6). The volume of menorrhagia can be quantitated, however, by the pictorial blood assessment chart (PBAC) (24). The PBAC is a chart which depicts the degree of pads or tampon saturation during a cycle, which when summed for weighted scores for light, moderate, or severe saturation, determines a PBAC score for each cycle (24). PBAC has shown good correlation with menstrual blood loss (25): a PBAC score of >100 strongly correlates with menstrual blood loss >80 cc,  $r=0.85$  (24), with 86% sensitivity and 89% specificity

(24), and, thus, is considered a quantitative marker of menorrhagia (25). PBAC may be used not only as a tool to diagnose menorrhagia, but also as a monitor of therapeutic response after intervention (26, 27). A logistic regression model demonstrated that > 80 cc menstrual blood loss is predicted by three variables, including the presence of clots >1 inch in diameter, low serum ferritin, and hourly pad/tampon change (23). Other nonspecific predictors of menorrhagia include i) bleeding severity score (3, 28, 29), ii) presence of flooding, iii) cycle duration >7 days, iv) anemia requiring treatment, v) family history of a bleeding disorder, and vi) excess bleeding with dental or surgical procedure, miscarriage or delivery (30). The latter four predictors, when coupled to PBAC >100, increase the sensitivity of PBAC to 95% (30). Finally, although the severity of nonspecific bleeding in VWD is measured by BSS, and BSS correlates with VWF:RCO level (3, 28, 29), neither PBAC nor menorrhagia severity appear to correlate with VWF levels (26, 27).

The lack of effective treatment for menorrhagia is a major unmet health need among women with bleeding disorders (5, 6), and as such constitutes a major public health problem (5, 17, 23). While 80% respond to DDAVP (desmopressin) (3, 31, 32), the first-line treatment for type 1 VWD, only 31% use it to treat menorrhagia (7), as intravenous infusion is inconvenient and the effect is short-lived, with depletion of endothelial VWF stores after three days (31). Response rates with intranasal DDAVP (Stimate®) are lower (32-35), related to its less potent effect on VWF release (31). Although hormonal therapy, specifically combined oral contraceptives (OC) are effective in 70% (36), their use is limited by headaches and hypertension (32, 36), and only 35% of women with bleeding disorders use these OC to treat menorrhagia (7). The levonorgestrel intra-uterine system (Mirena), which releases hormone into the endometrial cavity where it is absorbed has antifibrinolytic effect, reducing blood loss (37), but its use is limited by weight gain and depression in 20% (37). A recent prospective trial demonstrated the antifibrinolytic agent, tranexamic acid (Cyclokapron®, TA), was effective in reducing menstrual blood loss by PBAC score in up to 50%, although nausea was a common adverse event (27). TA is now the recommended non-hormonal agent of choice for menorrhagia (27, 38). A new recombinant VWF, rVWF (Vonvendi), licensed by the U.S. Food and Drug Administration for treatment of bleeding in von Willebrand disease, is a pure VWF protein with intact VWF subunits, produced in the absence of ADAMTS-13, the VWF cleaving protein, with a high ratio of high molecular weight and ultra large HMW multimers. This accounts for its increased potency over plasma-derived VWF (Humate P) (39), which is the current standard VWF concentrate. It is manufactured with no animal or human components. In a phase 1 trial rVWF was safe and well tolerated in those with type 3 VWD (8). In a recently completed phase 3 VWF efficacy and safety trial (9), rVWF was effective in treatment of 192 bleeds in 22 subjects with a response of excellent or good in 100%. There was bleed resolution in 81% of bleeds with a single dose, median 40-50 IU/kg, with the remainder resolving after a 2<sup>nd</sup> dose. rVWF was well tolerated with no thrombosis, allergic reaction or antibodies to rVWF.

Given the importance of clinical coagulation evaluation in women with menorrhagia (17, 22, 38), the high proportion of women with menorrhagia who have an underlying bleeding disorders (4-7), and the identified limitations of current therapies for women with bleeding disorders who have menorrhagia, there is consensus that better treatment approaches are needed to improve health outcomes and quality of life for women with VWD (3, 5, 38). As ineffective treatment remains the greatest unmet healthcare need among women with bleeding disorders (5, 38), which affects quality of care and cost of care, it is a

critical time to initiate a study to compare safety and efficacy of rVWF (8, 9) vs. TA (27), the current non-hormonal agent of choice for menorrhagia in women with VWD and menorrhagia. This is consistent with the Healthy People 2020 goal of promoting healthy outcomes, reducing morbidity, and improving quality of life, with safe and effective therapies for those affected by bleeding disorders (40). The purpose of the proposed Phase III trial will be to compare rVWF vs. TA to reduce menorrhagia in women with VWD. This trial will be an outpatient 24-week study conducted in 60 subjects (inflated to 66 for anticipated 10% dropout) from approximately 25 HTC sites (2-5 subjects locally). IRB protocols will be prepared and submitted at each of the study sites. Sites will receive study forms and assessment tools to complete and upload into a web-based data base maintained by the University of Pittsburgh Center for Research in Healthcare Data Center (CRHC DC). For this trial, the Center for Clinical Trials and Data Coordination (CCDC), which is part of the CRHC DC, will serve as the Data Coordinating Center (DCC). A manual of operations will provide standardized operating procedures, including enrollment, randomization, data forms, data and specimen collection, shipping, and data and safety monitoring reports. Pictorial bleeding assessment charts (PBAC) will be completed by study subjects (primary endpoint) and patient diaries will establish subject acceptance and adherence to the two intervention arms. Other data collected (secondary endpoints) will include cycle duration, cycle severity, quality of life questionnaires, a satisfaction survey, and a cost-effectiveness questionnaire.

Based on our survey and literature review indicating VWF is safe and effective in reducing VWD-related menorrhagia, we *hypothesize* that intravenous recombinant von Willebrand factor (rVWF) on day 1 of the menstrual cycle is more effective than oral tranexamic acid (TA) three times daily on days 1-5 of the menstrual cycle, in reducing menstrual blood loss and improving quality of life, despite its higher cost and more invasive route of administration. Bleeding severity by PBAC collected by each subject will be the primary endpoint.

## 2.3 RISK/BENEFIT ASSESSMENT

### 2.3.1 KNOWN POTENTIAL RISKS

#### ***Risk to Subjects***

There are risks associated with the study drug and having blood drawn. rVWF and TA will be administered during four consecutive menstrual cycles on days 1-5 of bleeding. All subjects will be asked to report any safety problems or side effects associated with administration of study drugs.

#### ***Risk of Blood Drawing***

There may be discomfort with drawing blood, which is common, occurring in up to 25%, or 25 in 100 people: this may include pain, lightheadedness, fainting, 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 assuming a recumbent position, i.e. lying on your back with your head flat and knees bent, if lightheaded.

***Risk of Allergic or Anaphylactic Reaction***

Allergic-type reactions are rarely reported for rVWF, although were more commonly reported at higher dose (e.g. 75 IU/kg, or about 2-fold higher than used in this study), and thus, the risk is expected to be uncommon, occurring in < 0.001% or less than 1 in 100,000 people. Allergic reactions for TA are expected to be rare in this study, occurring in <.001%, or less than 1 in 100,000 people. Allergic reactions could include chills, fever, nausea and vomiting, or rarely may include, in decreasing order of severity, death, anaphylaxis (life-threatening difficulty breathing), low blood pressure, heart beat irregularity, increase in body fluids, paresthesias (numbness or prickling sensation), urticaria (hives), chest tightness, rash, pruritus (itching), edema (swelling), fever, and/or chills. Should these symptoms 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. Subjects will be monitored for these symptoms. No one with a history of allergy (hypersensitivity), an allergic reaction or anaphylaxis associated with either recombinant von Willebrand factor (rVWF, Vonvendi®) or tranexamic acid (TA, Lysteda®) will be enrolled. Subjects will be monitored closely for early symptoms and signs of hypersensitivity reactions, including hives, generalized urticaria, angioedema, chest tightness, dyspnea, wheezing, faintness, hypotension, tachycardia, and anaphylaxis. Any subject who develops signs or symptoms of an allergic type reaction or anaphylaxis during administration of either study drug will immediately have that study drug stopped and appropriate medical care initiated.

***Risk of Thromboembolism/ Thrombogenicity***

Although rVWF and TA may increase coagulation factor levels, they are rarely, if ever, associated with the development of thromboembolic complications. There is the unlikely possibility, < 0.001%, or less than 1 per 100,000 people, that either drug could cause a clot in the vein (thrombosis) with swelling or pain; or a clot in the lung (pulmonary embolus) with dyspnea or hemoptysis. The use of oral contraceptives with TA may increase risk of venous thromboembolism, and thus will not be allowed during study. This risk will be very carefully monitored clinically. 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. Should a clot occur, treatment would primarily consist of stopping the study treatment and/or removing the line in which it was given, if that is the source of the clot, as soon as possible. Should a bleeding episode occur during the study period, the subject will be treated with DDAVP or other hemostatic agent prescribed by her physician.

***Risk of Bleeding Events***

Bleeding symptoms may occur in VWD unrelated to this study, usually with trauma, but sometimes spontaneously, without cause. Although unlikely, should a subject have any bleeding during the study, she may take her usual standard treatment, DDAVP or VWF concentrate, whichever is usually used.

***Risk of Pregnancy***

There are potential risks with 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 a subject chooses to be sexually active, she 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. 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 a subject chooses to be sexually active during this study, she must accept the risk that pregnancy could still result, exposing her to potential loss of pregnancy as well as other unknown effects on the developing fetus.

***Birth Control Statement***

If a subject becomes aware that that she is pregnant or becomes pregnant during the course of this research study, she 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 a subject does not become pregnant during this research study. Hormones (other than progesterone-only) or a birth control implant will not be allowed during this study because of thrombosis risk. 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.

***Risk of Inadvertent Disclosure***

Study participation and related data will be protected to maintain confidentiality. There is a possibility that the subject's personal information or genetic material could 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. In order to reduce risks of disclosure or breach of confidentiality, the research related documents, blood samples and clinical information stored in subject research files will be assigned an alphanumeric (letters and numbers) identifier (that do not contain personal identifiers). For this study, a linkage key for linking this number and the subject's name will be kept at each site under lock and key by the PI and his/her research staff.

***Breach of Confidentiality***

There is also a potential for possible risk of breach of confidentiality of collected information. To minimize this risk, study participation and related information will be protected to maintain confidentiality. Blood samples and clinical history will be assigned an alphanumeric identifier and the key for linking this number with subject identity will be kept at each site under lock and key by the PI and his/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, subject names will not be identified.



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### 2.3.2 KNOWN POTENTIAL BENEFITS

#### ***Potential Benefits***

The subjects will be under close supervision during the study period. After administration of rVWF or TA it is anticipated menstrual bleeding frequency will be decreased from the untreated state. For women with menorrhagia, it is already established rVWF and TA may reduce menstrual bleeding, but whether one agent is more effective or better tolerated than the other is not known.

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### 2.3.3 ASSESSMENT OF POTENTIAL RISKS AND BENEFITS

Every day clinicians encounter women with von Willebrand disease where a decision to treat menorrhagia must be made. However, clinicians do not know what to do because 1) randomized trials and observational studies have shown that non-hormonal therapies including the anti-fibrinolytic agent TA, and the hemostatic agents, VWF concentrate, are effective in reducing menorrhagia, but side effects, pill burden, and requirement for intravenous infusion have limited their use; 2) pathophysiological arguments can be made for using either of these agents; 3) observational studies indicate that although they are safe and reduce blood loss, these agents are in some only somewhat effective and there is concern about thrombosis risk when these agents are used in combination with hormonal therapy; and guidelines provide conflicting advice. This has led to practice variation and confusion in the clinical community with no clear guidance on safe, optimal treatment for menorrhagia. Based on these findings and existing data there clearly is equipoise. For all these reasons, a high quality randomized trial to guide treatment is urgently needed to answer this clinically relevant question. It has been already established that rVWF and TA each effectively and safely reduce menstrual bleeding, but whether one agent is more effective or better tolerated than the other is not known. The known risks of these agents include, rarely, thrombosis and allergic reaction.

The risks/ benefit ratio indicates the value of the information to be gained outweighs the potential risks of participation in the trial as 1) risks associated with rVWF and TA are low, importantly thrombosis risk is <0.4% with VWF, based on data from the literature; 2) individuals with cardiac disease, hypertension, MI, stroke, thrombosis, or seizure are excluded from the trial; and 3) precautions are in place to protect against potential risks, e.g. avoiding hormonal therapy or hormonal implants beginning 3 months before and during the trial; and avoiding pregnancy by requiring pregnancy tests on day 1 of each cycle before study drug can be taken. Thus, the risk/benefit ratio of participating in the trial outweighs the risk of gained outweighs the potential risks of participation in the trial.

### 3 OBJECTIVES AND ENDPOINTS

OBJECTIVES	ENDPOINTS	JUSTIFICATION FOR ENDPOINTS
<b>Primary</b>		
The <b>Primary Objective</b> is to determine the efficacy of rVWF vs. TA in reducing menorrhagia in women with VWD.	The <b>Primary Endpoint</b> is a 40-point reduction in PBAC after two cycles.	In a trial of TA 40% of women had a 50-point reduction in PBAC after 2 cycles, from a baseline PBAC score >100. As rVWF is i.v. and costs more than TA, we estimated rVWF would need to improve PBAC 40 points more than TA to be adopted into practice.
<b>Secondary</b>		
The <b>Secondary Objective</b> is to evaluate safety, tolerability, acceptability of rVWF vs. TA in reducing menorrhagia in women with VWD.	The <b>Secondary Endpoints</b> are cycle severity, cycle duration, and QoL by SF-36, Rute Menorrhagia Severity Scale, CDC-HRQoL-14, CES-D, and satisfaction survey.	Cycle severity and duration add descriptive detail to PBAC. Quality-of-life measures were used in past studies. The satisfaction survey assesses intravenous rVWF experience.
<b>Tertiary/Exploratory</b>		
An <b>Exploratory Objective</b> is to determine cost-effectiveness by comparing events prevented and cost differences after rVWF vs. after TA.	The <b>Exploratory Endpoint</b> is cost-effectiveness determined by intervention-specific SF-36 utility values, and by events prevented, e.g. days missed at work/school, iron infusion, RBC transfusion, ED/ hospitalization.	As rVWF cost is higher than TA, intervention and event costs will be estimated after each study drug, using CMMS and HCUP data, but may be underpowered by small sample size and short follow-up.

### 4 STUDY DESIGN

#### 4.1 OVERALL DESIGN

- **Hypothesis.** We hypothesize that intravenous rVWF given on day 1 of menses will be superior to oral TA given on day 1-5 of menses, during each of two consecutive menstrual cycles, in reducing menorrhagia in women with von Willebrand disease.
- **Phase.** This is a Phase III trial.

- **Trial Design.** This is a Phase III prospective, randomized, crossover trial.
- **Methods to minimize bias.** Subjects will have access to VNA, clinic, or infusion center if needed to infuse rVWF, and a second “rescue” dose of rVWF will be allowed, as per current practice for any bleed. There will be no discrimination by race nor ethnicity. If a woman has iron deficiency, she will be treated; if she has hypothyroidism, she will be referred for treatment. All study supplies, including study drug, diaries, tampons, and pads, will be provided at no cost.
- **Dose escalation or dose-ranging.** No dose escalation is planned during this trial.
- **Number of study groups/arms and study intervention duration.** There are two groups to be compared, Group 1, who will be randomized to take Arm A first, then Arm B; and Group 2, who will be randomized to take Arm B first, then Arm A. The study intervention duration is 2 consecutive menstrual cycles each for each agent. For rVWF, this will be day 1 of menstrual bleeding for 2 consecutive cycles; and for TA this will be day 1-5 of menstrual bleeding for 2 consecutive cycles. The order is randomized.
- **Single site or multi-site.** This is a multi-site trial, with approximately 25 U.S. hemophilia treatment centers.
- **Study intervention(s).** Subjects randomized to **Group I** will receive **Arm A** rVWF 40 IU/kg intravenously (IV) infusion on day 1 of each of two menstrual cycles, Cycles 1 and 2. They will then be crossed over to **Arm B**, TA 650 mg 2 tablets orally (po) three times daily on days 1-5 of each of two menstrual cycles, Cycles 3 and 4. Subjects randomized to **Group II** will receive **Arm B**, TA 650 mg 2 tablets orally (po) three times daily on days 1-5, for each of two menstrual cycles, Cycles 1 and 2. They will then be crossed over to **Arm A**, rVWF 40 IU/kg intravenously (IV) infusion on day 1 on each of two menstrual cycles, Cycles 3 and 4.
- **Interim Analysis.** No interim analysis is planned.
- **Stratification.** No stratification is planned.
- **Sub-studies.** No sub-studies are planned in this protocol.

## 4.2 SCIENTIFIC RATIONALE FOR STUDY DESIGN

As von Willebrand disease is a rare, orphan disease, we determined that a randomized, cross-over trial design would be feasible for this trial, and would provide adequate statistical power and allow each woman to serve as her own control. There was consensus by our Steering Committee that the design was feasible, including the dose of 40 IU/kg. A survey of MDs at the approximately 25 participating HTCs indicated agreement on our approach to compare rVWF with TA, and with use of a “rescue” dose of rVWF on day 2 of the cycle, if menorrhagia was unresponsive. A survey of women with VWD indicated the trial design was acceptable, including use of an intravenous drug. Finally, the HTC MDs estimated based on their current population well known to them, that they would have at least 75 subjects available over the next 4 years for enrollment, sufficient to achieve N=66 subjects (N=60 subjects, with up to 10%, N=6, for dropouts) for the trial.

## 4.3 JUSTIFICATION FOR DOSE

Intravenous rVWF is FDA-approved to treat and prevent bleeds in VWD, including menorrhagia. Limited data summarized in a recent review (11) indicate the median dose used in women treated with VWF (pdVWF, plasma-derived; or rVWF, recombinant VWF) was 43 IU/kg. In consultation with our Steering Committee after review of the literature indicating excellent/good efficacy with rVWF for this indication, with <0.4% thrombosis risk, there was consensus to study a dose of 40 IU/kg. TA is specifically approved for this indication at a dose of 1300 mg (2 tablets each of 650 mg) three times daily for day 1-5 of menstrual bleeding.

#### 4.4 END OF STUDY DEFINITION

A participant is considered to have completed the study if she has completed all phases of the study including the last visit or the last scheduled procedure shown in the Schedule of Activities.

## 5 STUDY POPULATION

### 5.1 INCLUSION CRITERIA

In order to be eligible to participate in this study, an individual must meet all of the following criteria:

1. Females 13-45 years of age.
2. Mild or moderate von Willebrand disease (VWF:RCo <0.50 IU/ml, past bleeding).
3. Menorrhagia and a PBAC >100 in at least one of the last two menstrual cycles.
4. Regular menses, at least every 21-35 days.
5. Willingness to have blood drawn
6. No prior history of an allergic reaction or anaphylaxis to rVWF or TA.
7. Willingness to avoid ASA and nonsteroidal anti-inflammatory agents (NSAIDS) during the study.
8. Willingness to comply with randomization to rVWF or TA study arms.
9. Willingness to keep a personal diary of menorrhagia bleeding frequency duration and severity by pictorial blood assessment chart, and any drugs or hemostatic agents taken.
10. Willingness to make 4 visits, undergo blood sampling for coagulation studies, and accept randomization of two therapies for each of four consecutive menstrual cycles, including an end-of-study visit.
11. Willingness to use “double-barrier” method of contraception during the study.

### 5.2 EXCLUSION CRITERIA

Unless otherwise specified, subjects will be excluded from study if any exclusion criteria exist:

1. Any bleeding disorder other than von Willebrand disease; or past thrombotic disease
2. Pregnant or lactating, or use of hormones (other than progesterone-only), or combined oral contraceptives, and contraceptive implants in past 3 months.
3. Platelet count < 100,000/ul.
4. Use of immunomodulatory or experimental drugs.

5. Surgery within the past 8 weeks.
6. Concomitant use of antiplatelet drugs, anticoagulants, dextran, aspirin or NSAIDs.
7. Treatment with DDAVP, cryoprecipitate, whole blood, plasma and plasma derivatives containing VWF within 5 days of study.
8. Inability to comply with study requirements.
9. Hypothyroidism as defined by elevated TSH.
10. Iron deficiency as defined by low serum ferritin, unless iron replacement has been initiated.
11. History of renal disease

### 5.3 SCREEN FAILURES

Participants who are consented to participate in the clinical trial, who do not meet one or more criteria required for participation in the trial during the screening procedures, are considered screen failures.

### 5.4 STRATEGIES FOR RECRUITMENT AND RETENTION

**Recruitment:** Females with mild or moderate VWD, age 13-45 years, defined by VWF:RCo < 0.50 IU/mL, previous bleeding history and menorrhagia defined by PBAC >100 in at least one of two preceding menstrual cycles, who fulfill the inclusion and exclusion criteria, and who are cared for at one of the approximately 25 HTC's participating in this trial *will be eligible for study*. Subjects approached for participation in this study will have VWD and be contacted during routine clinic visits to determine their interest in participating in the study. There will be no cold-calling. The Site PI will determine the patient's interest in study participation, and, if the patient is interested, the study will be discussed in further detail and the informed consent reviewed. Subjects will be encouraged to take time to decide on participation, and ask questions. If subjects decide to take a consent form home for further viewing, discussion will include the purpose, safety issues, and risks and benefits of the study. All questions will be answered prior to and obtaining informed consent. No experimental procedures or interventions will occur until after informed consent is obtained. The investigator's certification statement will be signed at the time consent is obtained. If any new information occurs during the conduct of the study, subjects who have been consented will be informed and will be re-consented with this information at the next visit. A de-identified prescreening/ screening log will be kept, and all reasons for exclusion documented in study source documents and screening log. Subjects who read the consent form are free to refuse enrollment, and participants will be free to withdraw at any time. If a subject wishes to withdraw, she may do so by addressing a letter to the principal investigator. Any data collected prior to the time of withdrawal will continue to be used, but no additional information will be collected. Processed blood sample results will continue to be used for the research study; however, remaining samples will be destroyed or used as indicated by subject's letter. The reason (e.g. AE, lost to follow-up, etc.) and date of withdrawal for all subjects withdrawn from this study will be recorded. Subject information obtained by electronic data capture will be stored and managed on the CRHC DC website. The NIH and IRB may inspect the records of this study. Every effort will be made to keep the subject's personal medical data confidential. Subject eligibility for the study will be determined prior to randomization and within 7 days of the first dose of

rVWF or TA. Subjects will sign informed consent. Subject screening and enrollment will be conducted by the local Investigator, in communication with the CRHC DC web-based data entry system. Subjects will be considered enrolled in the study after all assessments have been completed during the Screening period and just prior to Day 1 of study. No subject may begin treatment prior to enrollment and assignment of a unique subject identification number. Any subject identification numbers that are assigned will not be reused even if the subject does not receive treatment.

**Retention:** Retention *is a* critical issue for clinical trials in rare diseases: to mitigate against concern, blood draw is limited to the screening visit, and there are only 4 study visits which will be scheduled after menstrual cycles at a time convenient for the subject. Study drugs will be provided at no cost, and assessed after 2 menstrual cycles each, which has been shown to be as informative as after 6 menstrual cycles (26). rVWF may be given by self-infusion, or by HTC nurses who are trusted and have expertise in caring for VWD, and VNA will be available for home and weekend infusions. In addition, screening and managing iron deficiency and hypothyroidism will contribute to the health of these women. Finally, subjects will receive compensation for participation in this study, to help defray the cost of meals, travel, and time lost from work. The trial will enroll 60 women (inflated to 66 for anticipated 10% dropout), 13-45 years of age, recruited during HTC clinic from the approximately 25 U.S. participating HTCs, at a rate of 1 or more per HTC per year during the trial. There are no non-U.S. sites. There will be no discrimination based on race or ethnicity. Children under 13 as most have not reached regular menses and males will be excluded as they have no menstrual cycles.

## 6 STUDY INTERVENTION

### 6.1 STUDY INTERVENTION(S) ADMINISTRATION

#### 6.1.1 STUDY INTERVENTION DESCRIPTION

**Drug Information: Recombinant von Willebrand Factor (rVWF).** Recombinant rVWF (vonicog alfa, Vonvendi) is approved by the FDA for treatment or prevention of bleeds, including menorrhagia, in VWD. rVWF is produced by DNA technology. It is synthesized by a genetically engineered Chinese hamster ovary (CHO) cell line that co-expresses both VWF and FVIII genes (39). This is the first VWF manufactured and formulated in the absence of animal or other human plasma proteins, thus eliminating the theoretical risk of transmissible agents and other blood-borne pathogens. It has been established that the ultra large and high molecular weight multimers (HMWM) of VWF are essential for platelet plug formation (42). Unlike plasma-derived (pd) VWF concentrates which lack ULM due to in vivo proteolytic cleavage by the plasma VWF-cleaving protein, ADAMTS13 (a disintegrin and metalloprotease with a thrombospondin type 1 motif, member 13), rVWF has no exposure to ADAMTS13 during the production process and thus contains intact HMWM and ULM (39). The presence of ULM and the higher purity are associated with greater specific activity of rVWF, measured by VWF ristocetin cofactor activity (VWF:RCo) relative to VWF antigen (VWF:Ag). The pharmacokinetics of rVWF in patients with type 3 VWF were evaluated in a phase 1 clinical trial, which showed a longer terminal half-life for rVWF compared to pdVWF and stabilization of endogenous FVIII:C (8). ULMs present in rVWF underwent rapid proteolysis by endogenous ADAMTS13 and no thrombotic events were observed. A subsequent phase III trial recently completed (9)

demonstrated that rVWF is safe and hemostatically effective in severe type 1, 2, and 3 VWD patients for treatment of bleeds, including menorrhagia. There was a total of 192 bleeds in 22 subjects, with 96.9% rating bleed control excellent or good, according to a 4-point scale (4=none to 1=excellent). A single infusion was effective in 81.8% of bleeds. In addition, rVWF stabilized endogenous FVIII, and rVWF half-life was 21.9 hours, and factor VIII activity increase rapidly, achieving hemostatic levels within 6 hours of dosing. rVWF was well tolerated. There were serious adverse events in two subjects: chest discomfort and increased heart rate, not associated with any cardiac symptoms, and there were no thrombotic or severe allergic events, or antibodies to VWF or FVIII (9).

**Drug Information: Tranexamic Acid (TA).** Tranexamic acid (TA, Lysteda®) is currently approved by the FDA for treatment of menorrhagia (43). rVWF is currently approved by the FDA and will be supplied for use in this study by Shire Inc. Both drugs will be distributed by the NIH-contracted pharmacy and shipped to HTC participants in this study as randomization is assigned to enrolled subjects. TA is FDA approved and has been used for years with a long safety profile in subjects with bleeding disorders. rVWF is approved by the FDA for treatment of bleeding, including menorrhagia, in VWD. TA will be provided as two 650 mg tablets for a dose of 1300 mg three times daily for the first 5 days of menstrual bleeding.

**Administration of Study Drugs.** Once a subject is identified as eligible for the study and assigned the unique subject number by the CRHC DC Web-Based Data System, the individual preparing the rVWF and TA will first carefully review the accession number on each drug container or vial, for agreement with the accession number assigned to each individual study subject. rVWF will be available for intravenous administration in single-use vials containing approximately 650 or 1300 IU per vial, as a sterile, lyophilized powder. The 650 IU/vial is reconstituted with a 5-ml vial of sterile water for injection, USP; the 1300 IU/vial is reconstituted with a 10-ml vial of sterile water for injection. The resulting solutions for the individual 650 IU/vial and 1300 IU/vial have a pH of 7.3. A two-way needle will allow transfer of the diluent into the lyophilized powder for reconstitution and slow infusion over 5-10 minutes. Storage of rVWF post-reconstitution should be at room temperature not to exceed 25°C (77°F) for up to 3 hours. TA will be available for oral administration at a dose of two 650 mg tablets per dose. Details of the storage, lot number, stability, production and expiration dates for each drug, rVWF and TA, will be supplied by the contracted pharmacy, McKesson.

**Drug Records for Study Drugs.** This study site will maintain accurate records, demonstrating dates and amount of study treatment received, to whom dispensed (subject-by-subject accounting), and accounts of any study treatment accidentally or deliberately destroyed. McKesson will contract and coordinate the process of shipping rVWF and TA to each HTC. It is estimated that McKesson will make shipments of rVWF and TA to HTCs every 4 weeks. All pill containers and vials, both used and unused, must be saved for study treatment accountability. At the end of the study, reconciliation must be made by HTCs between the amount of study treatment supplied, and dispensed. Unused study drugs will be destroyed by study sites. A written explanation will be provided for any discrepancies. Unused study drug will be destroyed locally at the HTCs. There are no site monitoring visits planned at this time.

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### 6.1.2 DOSING AND ADMINISTRATION

**Route of Administration of Study Drugs.** rVWF dosing will be by study subjects (or VNA or HTC nurse) by standard intravenous technique, over 5-10 minutes or less, using a 5-10 cc syringe for injection into a vein. TA dosing will be by study subjects by oral self-administration. All drugs by study Group and Arm, rVWF or TA, will be taken at the same time each day, preferably beginning at 8 am in the morning.

**Dosing of Study Drugs.** rVWF will be given at 40 IU/kg by intravenous infusion over 5-10 minutes by standard intravenous technique into a vein on day 1 of menstrual bleeding or TA will be given as two 650 mg tablets (1300 mg) orally three times daily on the first 5 days of menstrual bleeding during each of 2 consecutive cycles in up to 60 women (inflated to 66 for anticipated 10% dropout). with VWD. All enrolled subjects will be randomized to one of two treatment arms and followed for up to 24 weeks. Follow-up visits will occur at week 16 (post cycle 2) and 24 (post cycle 4, end-of-study). All study visit timelines will add +/- one day to allow for weekends. Subjects randomized to rVWF will be trained in intravenous technique by study nurses, or can set up home visiting nurse for home self-injection. For bleeding not relieved after one dose, an additional dose may be given on the following day by HTC MD discretion.

## 6.2 PREPARATION/HANDLING/STORAGE/ACCOUNTABILITY

### 6.2.1 ACQUISITION AND ACCOUNTABILITY

**Distribution of Study Drugs.** For subjects enrolled on study, rVWF and TA will be shipped from the contracted pharmacy, McKesson, to participating HTCs. McKesson will prepare study drug for each study subject, per randomization code via web-based accession number, package, and ship to HTCs for study subjects. HTCs will store study drugs at 2-8°C until they are given to study subjects during study visits. Any subsequent shipments required will be arranged in the same manner by McKesson to the respective study sites, utilizing an accession number assigned by the Data Coordinating Center (DCC), to each vial and to each subject, according to treatment arm, which will be linked to the randomization code. McKesson will ship a 4-month supply of the study drugs, rVWF and TA, overnight with a temperature recording device to HTCs. rVWF will be shipped in the configuration of a vial of lyophilized powder and a matching vial of diluent; TA will be shipped as oral tablets in screw top bottles. The study drugs will then be packaged by McKesson for each study subject per randomization code. The HTC nurse will inspect each shipment and affix a computer-generated label to study drugs per the randomization code. Included in the shipments to HTCs will be forms describing the shipment, total number of bottles and/or vials being shipped, and the date of shipment. Study subjects will return all unused vials of study treatment to the HTC which will be subsequently destroyed per local procedures.

### 6.2.2 FORMULATION, APPEARANCE, PACKAGING, AND LABELING

**Formulation and Packaging of Study Drugs.** rVWF is formulated as a vial of lyophilized powder and a matching vial of diluent; the solution should be clear or slightly opalescent in appearance. TA is formulated as a white oval-shaped tablet, non-scored, provided in screw top bottles. Study drugs for each cycle will be packaged by McKesson for each study subject per randomization code and shipped to HTCs. The HTC nurse will inspect each shipment and affix a computer-generated label to study drugs per the



randomization code. A 4-month supply will be shipped together, with clarification based on randomization, which drug is taken during Cycle 1 and 2, and which drug is taken during Cycles 3 and 4.

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### 6.2.3 PRODUCT STORAGE AND STABILITY

**Storage and Stability of Study Drugs.** HTC will be responsible for immediately opening the shipment of rVWF and TA, upon receipt and removing temperature recording devices from the shipment. The temperature information will be recorded as requested on the shipping form provided by each distribution center. HTCs will also visually inspect the vials to ensure no damage to bottles or vials occurred during shipment and physically count the number of bottles and vials received. This information will be recorded on the forms provided in the shipment by the distribution centers. If there are any discrepancies, the distribution centers will be notified immediately and further action taken at that time. HTC sites will store packaged, labeled study drug (rVWF) at 2-8°C and room temperature (TA) until distributed to study subject at study visits. rVWF is stable refrigerated at 2°C to 8°C in the original box and must be protected from extreme exposure to light: it is stable typically up to 2 years, per the label. Once reconstituted, if not used, it may be stored at room temperature not to exceed 25 °C (77 °F) for up to 3 hours. TA is stable at room temperature for up to 2 or more years.

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### 6.2.4 PREPARATION

**Preparation of Study Drugs.** rVWF is a lyophilized powder that must be reconstituted with Sterile Water for Injection (diluent), by two-way needle, inverting diluent over the vial of powder. Once transfer is complete, the contents of the vial are gently swirled to completely dissolve the powder. It must not be shaken. Once completely dissolved, the contents of the vial are drawn up into a syringe, after which it is infused intravenously at a rate of up to 4 ml per minute.

TA requires no preparation.

## 6.3 MEASURES TO MINIMIZE BIAS: RANDOMIZATION AND BLINDING

**Randomization of Study Drugs.** Following confirmation of the subject's eligibility along with the subject identification number, the study randomization will be assigned in a 1:1 fashion, and an accession number linked with the randomization schema in the database and used for all subsequent study drug allocation. Randomization could occur within 72 hours of screening. Study drugs rVWF and TA will be prepared and shipped by McKesson to participating HTCs. McKesson will prepare study drugs for each subject based on randomization assignment, linked through the CRHC DC web-based data system and shipped to participating HTCs for each study subject, where study drugs will be stored at 2-8°C until they are given to study subjects. Pending HTC receipt of study drug shipment, the 24-week trial will begin with the first menstrual cycle following randomization. If the subject has a bleed requiring hemostatic agent treatment after screening or for other reason, which delays the start of study for greater or equal to 6 months, the screening tests must be repeated and a re-verification of eligibility must also take place. Subjects will take the assigned study drug for the first day (rVWF) or the first 5 days (TA) of menstrual bleeding during each

of the next 4 consecutive menstrual cycles, with the first assigned study drug for the first 2 menstrual cycles, Cycles 1 and 2, followed by crossover to the alternative study drug for the next 2 menstrual cycles, Cycles 3 and 4.

**Minimization of Bias.** Subjects will be enrolled on the trial based on the investigator verification of eligibility, unbiased by race or ethnicity, and recognizing that drug and study arm assignment will be performed by the DCC randomization schema. See Demographic Chart below.

**Blinding.** Not applicable.

**Demographic Chart: Targeted Enrollment for Study**

TARGETED/PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	Sex/Gender		
	Females	Males	Total
Hispanic or Latino	2	0	2
Not Hispanic or Latino	58	0	58
<b>Ethnic Category: Total of All Subjects *</b>	60	0	60
Racial Categories			
American Indian/Alaska Native	0	0	0
Asian	6	0	6
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	9	0	9
White	45	0	45
<b>Racial Categories: Total of All Subjects *</b>	60	0	60

\* The "Ethnic Category: Total of All Subjects" must be equal to the "Racial Categories: Total of All Subjects."

#### 6.4 STUDY INTERVENTION COMPLIANCE

**Compliance.** Compliance with study drug will be assessed by patient diary and drug log maintained by study subjects during trial and reviewed by study nurses after each of 2 menstrual cycles on rVWF and on TA, during visits at the HTC, and also by the electronic database will also maintain track of drug adherence, including missed doses.

#### 6.5 CONCOMITANT THERAPY

**Concomitant Medications.** Medications taken during the trial will be obtained by medical history, including any hemostatic therapy and any other bleeds which may occur during the trial. Bleeds at other mucosal sites including epistaxis or gastrointestinal bleeding, which may occur but are unexpected in those with VWD, will be recorded on the diary and concomitant medication form. For this protocol, a

prescription medication is defined as a medication that can be prescribed only by a properly authorized/licensed clinician. Medications to be reported in the Patient Diary are concomitant prescription medications, over-the-counter medications and supplements.

### 6.5.1 RESCUE MEDICINE

**Rescue Dose of Study Drug.** As is standard in clinical practice for any bleed, subjects on this trial will be allowed to receive a second “rescue” dose of rVWF for menorrhagia on day 2 of either or both of two cycles for which they are randomized to rVWF, for inadequately controlled menstrual bleeding. The rescue dose will be given in the same dosage as the rVWF dose given on day 1 of the two cycles for which they are randomized to rVWF. They will record this in their patient diary and report it to the study nurse during follow-up visits.

## 7 STUDY INTERVENTION DISCONTINUATION AND PARTICIPANT DISCONTINUATION/WITHDRAWAL

### 7.1 DISCONTINUATION OF STUDY INTERVENTION

**Discontinuation/withdrawal.** All subjects who discontinue study drug will remain on study for follow-up, especially for safety and efficacy study endpoints. Reasonable efforts will be made to undertake protocol-specified procedures to capture adverse events (AE), serious adverse events (SAE), and unanticipated problems (UPs). The date and specific underlying reason for each discontinuation or withdrawal will be captured by a separate case report form.

**Considerations for Stopping the Trial.** It is possible that the test statistic will cross the monitoring boundary. Statistical interim monitoring results should be taken as one component to the decision as to whether or not to stop a trial. To stop the trial for efficacy, results should be definitive enough to be able to change clinical practice. The DSMB will use the monitoring information to determine its recommendation to NHLBI. The DSMB can recommend that the trial should continue as proposed, that the protocol should be modified based on the results seen in one treatment comparison or in some well-defined subgroup of patients, or that the trial should be terminated early. The final decision to stop trial rests with the NHLBI. If recommendation is to stop the trial, the trial principal investigators shall be consulted before a final decision is made.

We will allow the trial to run to completion if the intervention appears at least as effective as standard TA therapy. We propose halting the trial if a safety event reaches any stopping rules: (i) uncontrolled menstrual bleeding; (ii) thrombosis; or (iii) or grade 2-5 allergic reactions. Please see section 9.4.4. The DSMB will review each event to determine if the trial should be halted. Statistical interim monitoring results should be taken as one component to the decision as to whether or not to stop a trial. To stop the trial for efficacy, results should be definitive enough to be able to change clinical practice. The DSMB will use the monitoring information to determine its recommendation to NHLBI. The DSMB can

recommend that the trial should continue as proposed, that the protocol should be modified based on the results seen in one treatment comparison or in some well-defined subgroup of patients, or that the trial should be terminated early. The final decision to stop trial rests with the NHLBI. If recommendation is to stop the trial, the trial principal investigators shall be consulted before a final decision is made.

### **Suspension and Stopping Rules**

According to the protocol Safety Stopping Rules, the trial will be terminated if an event(s) reach any stopping rules. A terminated trial means no further subjects are enrolled or treated. If an event(s) trigger any suspension rules, the study will put on hold until the DSMC and Medical Monitor evaluate the event and make a final recommendation. A suspended trial means no further subjects are enrolled, but already enrolled subjects will be treated. In addition, all subjects who develop inhibitors, no matter the treatment they receive, will be monitored.

## **7.2 PARTICIPANT DISCONTINUATION/WITHDRAWAL FROM THE STUDY**

**Discontinuation/ Withdrawal.** Study subjects are free to withdraw from participation in the study at any time upon request. An investigator may discontinue or withdraw a participant from the study for the following reasons:

- Pregnancy
- Significant study drug non-compliance
- If continued participation in the trial, e.g. because of any clinical adverse event, laboratory abnormality, or other medical condition or situation would not be in the best interest of the subject
- If the subject meets an exclusion criterion (either newly developed or not previously recognized) that precludes further study participation, e.g. elevated TSH indicating hypothyroidism
- If the subject is unable to receive study drug for the prescribed duration, and/or complete it.

The date and specific reason for participant discontinuation or withdrawal from the study will be recorded on a separate Case Report Form. Subjects who sign the informed consent form and are randomized but do not receive the study intervention may be replaced. Subjects who sign the informed consent form, and are randomized and receive the study intervention, and subsequently withdraw, or are withdrawn or discontinued from the study may also be replaced. It is anticipated that up to 10% (6) subjects will discontinue or drop out of the trial; thus, 66 subjects will be enrolled to assure 60 subjects complete it.

## **7.3 LOST TO FOLLOW-UP**

**Lost to Follow-up.** Study subjects will be followed for a total of 24 weeks during the trial. Validity of the study is at risk when subjects are lost to follow-up, as information for endpoint documentation and evaluation is then lost. A study subject will be considered lost to follow-up if she fails to return for a scheduled visit and is unable to be contacted by the study site staff.

The following actions must be taken if a participant fails to return for a required study visit:

- The site will attempt to contact the participant and reschedule the missed visit within 4 weeks and counsel the participant on the importance of maintaining the assigned visit schedule and ascertain if she wishes to and/or should continue in the study.
- Before a subject is deemed lost to follow-up, the investigator will make every effort to regain contact with the subject, including up to 3 telephone calls and, if necessary, a certified letter to the subject's last known mailing address or local equivalent methods. These contact attempts will be documented in the subject's study file.
- Should the subject continue to be unreachable, she will be considered to have withdrawn from the study with a primary reason of lost to follow-up.

## 8 STUDY ASSESSMENTS AND PROCEDURES

### 8.1 EFFICACY ASSESSMENTS

- This section includes a list and description of the efficacy assessments to be conducted on the trial.
- **PBAC Score.** The PBAC will be scored for the 2 previous menstrual cycles and as the primary efficacy outcome of the trial for each cycle on the trial. PBAC at screening will be scored by the subject to determine eligibility, which per definition of menorrhagia, requires the PBAC score be >100 for at least one of two previous menstrual cycles. If the PBAC is not above 100 in past two cycles, this constitutes exclusion from participation. PBAC for each cycle, including Cycle 1 and 2 on study drug (either rVWF or TA) will be compared to PBAC for cycles 3 and 4 on study drug (either TA or rVWF).
- **Cycle Severity Rating (CS) and Cycle Length (CL).** The cycle severity (CS) and cycle length (CL) will be rated by numeric scale 0-3, and recorded in diaries. This will rate the severity of each cycle by a single score: ratings include: 0=mild bleeding much less than usually experienced; 1=moderate bleeding less than usually experienced; 2=moderately severe bleeding but not as bad as the worst menstrual bleeding experienced; and 3=severe bleeding, as bad as the worst menstrual bleeding experienced. Cycle length (CL) will be in days of tampon/pad use on PBAC. These measures will provide more subjective ratings than PBAC, and as such, will provide distinct data separate from the primary endpoint.
- **Quality-of-Life Questionnaires.** The impact of the two study interventions on quality of life will be determined by SF-36, Ruta Menorrhagia Severity Score, CDC-HRQoL-14, and CES-D, measured at baseline, and after the first two cycles (Visit 3), and after the second two cycles (Visit 4). The **Short-Form-36 (SF-36)** is a 36-item general health survey in eight areas of physical and mental health (67, 68), which has been validated in women of reproductive age and strongly associated with VWD phenotype: lower SF-36 scores correlate with higher bleeding scores (69). The **Ruta Menorrhagia Severity Scale** is a 15-item instrument that measures the physical,

psychological and social effects of menorrhagia (70), and is validated for menorrhagia: higher scores correlate with reduced PBAC (13). The **CDC Health-Related Quality of Life (HRQoL-14)** is a 14-item instrument that assesses “healthy days” including the number of physically and mentally unhealthy days in the past 30 days, and has been standardized for women of reproductive age (71). The Center for Epidemiology Studies Depression (CES-D) Scale is a 20-item screen for depression that identifies depression symptoms over a range of ages and demographic groups (72). It is expected that QoL score by these 4 scales will improve with study drugs and correlate with the reduction in menorrhagia by PBAC score.

- **Satisfaction Survey.** A Satisfaction Survey will be assessed after two cycles of rVWF in which subjects will a) rate treatment with rVWF as compared with their usual treatment of heavy menses; b) rate how difficult or problematic the use of rVWF was; and c) indicate if rVWF will be considered for use in future menstrual cycles. It is anticipated that if rVWF results in no better improvement than TA, satisfaction will be lower, and the use of rVWF may not be justified.
- **Cost-Effectiveness Questionnaire.** Given rVWF burden (IV route, cost), we will collect cost-effectiveness data (i.e. days lost from work/school, and need for iron infusion, RBC transfusion, or ER or hospital care) and compare events prevented and cost savings after 2 cycles on each treatment. Intervention and event costs will be estimated using data for Centers for Medicare and Medicaid Services (CMMS) and Healthcare Cost Utilization Project (HCUP) (73). The effectiveness term in the analyses will be intervention-specific SF-36 QoL utility values (74). Data will also be compared by general estimating equations (75), which may be underpowered by the small sample size and short trial follow-up (76), and thus, will be an exploratory endpoint.

Please refer to MOP for detailed description of study procedures.

## 8.2 SAFETY AND OTHER ASSESSMENTS

This section includes a list and description of the safety assessments to be conducted on the trial.

- **Screening Laboratory Evaluations.** Baseline laboratory studies will be drawn at screening, including Blood Counts: hemoglobin, platelets; Iron Tests: iron, TIBC, ferritin; Thyroid Test: TSH; and Von Willebrand Tests (VWF:RCo (activity), VWF:Ag, VIII:C, multimers, and VWF genotype). Before initiating treatment, subjects will be trained by the HTC nurse on 1) reading urine pregnancy tests and 2) completion of the pictorial blood assessment chart (PBAC), cycle severity rating (CR), and cycle length (CL); and 3) completion of patient diary. The Blood Counts, Iron Tests, and Thyroid Test will be performed by Quest laboratories. Any subject who has hypothyroidism, defined by an elevated TSH; or who has iron deficiency as defined by low serum ferritin, if untreated, are ineligible. If the MD initiates iron therapy in a patient with low serum ferritin, she is eligible to participate on the trial. The VWF Assays will be performed at the University of North Carolina FOBR laboratories, Chapel Hill NC, and the VWF genotype will be performed by Functional Bioscience, Madison WI. These laboratories are in compliance with and have on record updated Clinical Laboratory Improvement Amendments (CLIA) certificates. The Table below lists for each of the specific laboratory assays, the estimated volume and type of specimen needed for

each test, conditions for specimen preparation, shipping, and the laboratory receiving the sample and performing the assay.

- **Urine Pregnancy Test.** A urine HCG pregnancy test will be performed by each subject at baseline and at the onset of menstrual bleeding in each of 4 cycles during the trial. Study drugs may be used only after a negative urine pregnancy test. Nurses will train subjects in how to administer and read the test. If the test is positive, subjects may not take study drugs, and must notify their HTC and physician and nurse immediately.
- **Brief Medical History, Vital Signs, and Physical Examination:** To establish baseline status, a brief medical history, physical exam, and vital signs will be obtained. The medical history will include all medical diagnoses, surgeries, current medications, concomitant medications, and any allergies. Vital signs will include temperature, pulse, respirations, blood pressure, height, and weight. The physical exam will include targeted HEENT, chest, abdomen, extremities, neurologic, and skin assessment. Subsequent visits will assess interval change by interim history and vital signs.
- **Patient Diary and Drug Log.** The Patient Diary will capture information collected by the study subject, including the PBAC score, cycle severity (CS), cycle duration (CSL), other bleeds and use of “rescue” dose of rVWF. The drug log will keep track of dose and frequency of study drugs taken, any missed doses, date and reason for missed doses, and adherence to study drug.
- **Assessment of Adverse Events.** The provisions for follow-up of ongoing AEs/SAEs will include monitoring all subjects for allergic reactions, thrombosis, or uncontrolled bleeding. Any adverse events will be monitored by the HTC physician until resolution of each AE or SAE. The degree of relatedness to study drugs will be determined, duration of adverse event, any medication given to treat the subject, and time to resolution of the event.
- **Availability of Lab Results to Subjects.** The results of Blood Counts, Iron tests, and Thyroid Tests will be made available to study subjects, and will establish eligibility. The results of the VWF assays and multimers, and VWF genotype will be used for research purposes only, to compare with PBAC scores by study arm. As previously noted, a subject’s medical chart or results of diagnostic tests performed as part of individual regular medical care may be used for screening or as a part of data collection. Therefore, the Health Insurance Portability and Accountability Act (HIPAA) rules, other relevant federal or state laws, and local institutional requirements will be followed, as applicable. Information regarding past VWD diagnosis, and PBAC score from past menstrual cycles will be reviewed to help determine eligibility.

Lab Assay	Tests	Volume/Type Tube	Preparation/Shipping/ Laboratory
Blood Counts	Hemoglobin, platelets	One 4.0 ml EDTA purple top	No preparation for EDTA tube. Ship ambient by Fed Ex to: Quest Diagnostics, 875 Greentree Road, Four Parkway Center, Pittsburgh PA, 15220.
Iron Tests	Iron, TIBC, ferritin	One 4.0 ml SST tube	No preparation for SST tube. Ship ambient by Fed Ex to Quest Diagnostics, as above.
Thyroid Tests	Thyroid stimulating hormone (TSH)	(part of SST tube above)	No preparation for SST tube. Ship ambient by Fed Ex to Quest Diagnostics, as above.

VWF Assays	VWF:RCo, VWF:Ag, FVIII:C, multimers	Three 5.0 ml CITRATE blue top tubes	Spin 15 minutes at 3000 rpm (1300 g), at 4°C. Transfer plasma to 15 ml conical tube and spin for 7 minutes at 3000 rpm (1300g), at 4°C or room temperature. Aliquot into 4 x 200 µl cryovials and freeze at -70°C to -80°C until shipped overnight, frozen by Fed Ex to Dr. Tim Nichols, FOBRL, UNC 125 University Lake road, Chapel Hill NC 27516.
VWF Genotype	VWF genotype	One 5.0 ml EDTA purple top tube	Ship ambient by Fed Ex to Mr. Mike Meyer, ITxM Coagulation Laboratory, 3636 Boulevard of the Allies, Pittsburgh PA 15213. Samples will be batched and sent at end study to Functional Bioscience, 505 South Rosa Road, Suite 238, Madison WI 53719.

## 8.3 ADVERSE EVENTS AND SERIOUS ADVERSE EVENTS

### 8.3.1 DEFINITION OF ADVERSE EVENTS (AE)

An **Adverse event** (AE) is defined as an untoward or unfavorable medical occurrence in a human participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with a person's participation in the research, whether or not considered related to a person's participation in the research (21 CFR 312.32 (a)).

### 8.3.2 DEFINITION OF SERIOUS ADVERSE EVENTS (SAE)

A **Serious Adverse Event** (SAE) is defined as an adverse event that meets **any** of the following criteria:

- results in death;
- is life-threatening i.e. places a subject at immediate risk of death from the event as it occurred;
- requires inpatient hospitalization or prolongation of existing hospitalization;

*The latter is not regarded as an SAE if:*

- (i) The admission results in a hospital stay of less than 12 hours; OR
- (ii) The admission is pre-planned, i.e. scheduled surgery arranged prior to study; OR
- (iii) The admission is not associated with an AE (e.g. social hospitalization for respite care)

NB: *An invasive procedure during any hospitalization may be reported as an SAE*

- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; OR
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the subject's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

### 8.3.3 CLASSIFICATION OF AN ADVERSE EVENT

#### 8.3.3.1 SEVERITY OF EVENT

##### Classification of Adverse Events



Severity. The severity of the adverse event refers to the intensity of an event and is categorized as:  
Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated,  
Moderate; minimal, local or noninvasive intervention indicated; limiting age- appropriate instrumental activities of daily living,  
Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living,  
Life-threatening consequences; urgent intervention indicated,  
Death related to AE.

As an alternative, standard grading may be used, e.g. CTCAE, grade 1 to grade 5. If used, a “translation” between the CTCAE system and the standard grading above will be provided.

### 8.3.3.2 RELATIONSHIP TO STUDY INTERVENTION

**Relationship.** Relatedness refers to the extent to which an adverse event is considered to be related to the intervention or study procedures. An adverse event is considered **related** if there is a reasonable possibility that the event may have been caused by the procedure. Note that the term “**suspected**” is also means possibly, probably or definitely related to the intervention or study procedures. The following definitions apply to relatedness:

1. Unrelated
  - Adverse event is clearly due to extraneous causes (e.g., underlying disease, environment)
2. Unlikely (adverse event **must meet 2** of the following):
  - Does not have temporal relationship to intervention
  - Could readily have been produced by the participant’s clinical state
  - Could have been due to environmental or other interventions
  - Does not follow known pattern of response to intervention
  - Does not reappear or worsen with reintroduction of intervention
3. Possible (adverse event **must meet 2** of the following):
  - Has a reasonable temporal relationship to intervention
  - Could not readily have been produced by the participant’s clinical state
  - Could not readily have been due to environmental or other interventions
  - Follows a known pattern of response to intervention
4. Probable (adverse event **must meet 3** of the following):
  - Has a reasonable temporal relationship to intervention
  - Could not readily have been produced by the participant’s clinical state or have been due to environmental or other interventions
  - Follows a known pattern of response to intervention
  - Disappears or decreases with reduction in dose or cessation of intervention

5. **Definite** (adverse event **must meet all 4** of the following):
- Has a reasonable temporal relationship to intervention
  - Could not readily have been produced by the participant's clinical state or have been due to environmental or other interventions
  - Follows a known pattern of response to intervention
  - Disappears or decreases with reduction in dose or cessation of intervention and recurs with re-exposure

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#### 8.3.3.3 EXPECTEDNESS

**Expectedness.** An **unexpected** event is one that has not been documented previously as an established adverse reaction to the study intervention and that is not recognized as part of the natural progression of the disease. A particular event may also be considered unexpected if it has a higher severity grade than what has been documented or identified previously.

**Action:** Any action taken while on study drug to resolve the AE is to be documented as follows:

- Drug withdrawn
- Drug interrupted
- Dose not changed
- Dose increased
- Not applicable

**Outcome:** The outcome of the AE is to be documented as follows:

- Not recovered/resolved
- Recovered/resolved
- Recovered with sequelae
- Recovering/resolving
- Fatal
- Unknown

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#### 8.3.4 TIME PERIOD AND FREQUENCY FOR EVENT ASSESSMENT AND FOLLOW-UP

**Data Collection Procedures for Adverse Events.** The clinical site staff will report all SAEs on the trial data collection forms. Expected serious adverse events are listed in the manual of operations; these events are recorded on the in-hospital and the 30-day follow-up data collection forms. Site personnel are required to report and document all unexpected SAEs and UPs to the DCC. The DCC will send unexpected SAEs (as reported by the site) to the study Medical Monitor for final assessment of severity, relatedness, and expectedness.

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#### 8.3.5 ADVERSE EVENT REPORTING

**Reporting Procedures.** All reported SAEs and unanticipated problems will be included in systematic reporting to the DSMB on a semi-annual basis. This includes adverse events and problems previously transmitted through expedited reporting. The following three classes of events will be reported to the NHLBI, the DSMB and the local IRB in an expedited manner: 1) Fatal or life threatening unexpected

suspected SAE, 2) Non-fatal, non-life threatening unexpected suspected SAE, and 3) Unanticipated problem. Fatalities related to blood transfusions must be reported to the FDA within 7 days according to guidance: (<http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm074947.htm>). If a particular SAE is reported with abnormally high frequency during the trial, this will be submitted to the Medical Monitor at NHLBI for review. Site personnel will complete and submit an SAE form to the DCC within 24 hours of learning of the event whenever the event is both serious and unexpected. In cases where the event is not serious but places the patient at greater risk of physical, psychological, economic, or social harm, and is both unexpected and related to the study, the sites will notify the DCC within 14 days of learning of the event. SAE forms will be forwarded along with relevant patient history data to the Medical Monitor for review. The study Medical Monitor will assess severity, relatedness, and expectedness of the event within 48 hours.

**DCC Reporting for Study Sites.** Following the Medical Monitor's feedback, the DCC will complete an SAE report for adverse events categorized as serious, unexpected and related and submit the SAE within 72 hours of learning of the event to the NHLBI Project Officer and to the DSMB Executive Secretary. The DCC will also send a final (or updated) report by 7 days of learning of the event. A report will also be sent for unanticipated problems. The DCC will send the reports to the NHLBI DSMB Executive Secretary and the NHLBI Medical Monitor for review. All reporting from the time that the Site learns about the event until it is reported to the NHLBI, DSMB, FDA and IRBs will follow the NHLBI DSMB established timelines as specified in (<https://www.nhlbi.nih.gov/research/funding/human-subjects/adverse-event>) and shown above. Upon receipt of an expedited report, the DSMB chair will decide whether the event should be discussed at the next scheduled DSMB meeting or discussed as soon as possible at an ad-hoc meeting.

**Reporting of Local IRB Actions.** All adverse events experienced by study subjects from the time of dosing until 30 days after administration is to be recorded on the CRF, regardless of the severity of the event or its relationship to study treatment. The serious AE reporting procedures are based on the "Cancer Therapy Evaluation Program: Common Terminology Criteria for Adverse Events" (CTCAE) (49). Subjects will report any AE or SAE to the HTC co-investigator or nursing coordinator. All AEs, regardless of severity, will be followed up by HTC Investigator until satisfactory resolution. All subjects experiencing AEs using investigational product, will be monitored until symptoms subside and any abnormal laboratory values have returned to baseline, or until there is a satisfactory explanation for the changes observed, or until death, in which case a full pathologist's report will be supplied, if possible. Withdrawal from the clinical study and therapeutic measures shall be at the discretion of the investigator. IRB actions regarding the trial will be communicated to the NHLBI Project Officer and NHLBI Executive Secretary in an expedited fashion. If the IRB or ethics board at any site, CCC or DCC takes action regarding the trial (e.g., the IRB places a hold on the trial or suspends the trial), the site will report this to the CCC within 24 hours of the action. The Site will submit written documentation from the IRB, an explanation of the circumstances, and a plan of action to the CCC within 72 hours. The CCC will promptly communicate this information to the DCC and the NHLBI project officer and DSMB Executive Secretary.

**Adverse Event Reporting Period.** All randomized patients will be followed for 24 weeks. Reporting of AEs will cease at the conclusion of the trial.

### 8.3.6 SERIOUS ADVERSE EVENT REPORTING

See Table.

### 8.3.7 REPORTING EVENTS TO PARTICIPANTS

Reporting of adverse events to study subjects will follow Informed Consent guidelines, to assure subjects are aware of risks and benefits, and any event that might change the balance of risks and benefits.

### 8.3.8 EVENTS OF SPECIAL INTEREST

Not applicable.

### 8.3.9 REPORTING OF PREGNANCY

Study subject will perform a urine pregnancy test on the first day of menstrual bleeding for each of 4 cycles on study. If the test is positive, no study drug may be taken, and the result of the pregnancy test must be reported immediately to the physician.

## 8.4 UNANTICIPATED PROBLEMS

### 8.4.1 DEFINITION OF UNANTICIPATED PROBLEMS (UP)

An **Unanticipated Problem (UP)** is defined as any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency, taking protocol research procedures and participation population characteristics into consideration.
- Related or possibly related to a person's participation in the research.
- Places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

### 8.4.2 UNANTICIPATED PROBLEM REPORTING

See Table.

TABLE: NHLBI Serious Adverse Event and Unanticipated Problems Reporting Timelines

What Event is Reported	When is Event Reported	By Whom is Event Reported	To Whom is Event Reported
Fatal or life-threatening unexpected, suspected serious adverse reactions	Within <b>24 hours</b> of event.	Investigator	DCC, Local/Internal IRB
	Within <b>72 hours</b> of event.	DCC	NHLBI, DSMB
	Within 7 calendar days of event	DCC	NHLBI, DSMB
	Within <b>15 calendar days</b> of initial receipt of information	Investigator	DCC, Local/internal IRBs

Non-fatal, non-life-threatening unexpected, suspected serious adverse reactions		Sponsor	FDA, All investigators
Unanticipated Problem that is not an SAE	Within <b>14 days</b> of the investigator becoming aware of the problem	Investigator	DCC, Local/internal IRBs NHLBI, DSMB
All Unanticipated Problems <sup>2</sup>	Within <b>30 days</b> of the IRB's receipt of the report of the UP from the investigator.	IRB	OHRP
		Investigator <sup>3</sup>	External IRBs

1. Designee is appointed by the sponsor; for example, DCC, CRO.

2. Per OHRP guidance: only when a particular AE or series of AEs is determined to meet the criteria for an UP should a report of the AE(s) be submitted to the IRB at each institution under the HHS regulations at 45 CFR part 46. Typically, such reports to the IRBs are submitted by investigators.

3. Investigators should also take into account local IRB guidance if reporting timelines for UPs are shorter than OHRP guidance.

### 8.4.3 REPORTING UNANTICIPATED PROBLEMS TO PARTICIPANTS

Reporting of unanticipated problems to study subjects will follow Informed Consent guidelines, to assure subjects are aware of risks and benefits, and any event that might change the balance of risks and benefits.

## 9 STATISTICAL CONSIDERATIONS

### 9.1 STATISTICAL HYPOTHESES

There will be a formal Statistical Analysis Plan (SAP), completed prior to database lock and unblinding of the study data. Please refer to the SAP for additional information.

The primary endpoint is the pictorial blood assessment chart (PBAC) score, a validated measure of menstrual blood loss. PBAC scores from all four periods of the crossover trial (AABB/BBAA) will be utilized in statistical analyses. The null hypothesis is that there will be no difference in PBAC score improvement from baseline between intravenous rVWF and oral TA treatments. Our alternative hypothesis is that rVWF will be superior, producing a greater improvement in PBAC score compared to treatment by oral TA. Specifically, we hypothesize that intravenous rVWF will improve PBAC score by at least 40 points more than TA.

The secondary endpoints include frequency of menorrhagia unresponsive to study drugs or rescue, by Patient Diary, Drug Logs, Cycle Severity Rating (CS), Cycle Length (CL), Quality-of-Life (QoL) forms, including SF-36, Ruta, CDC-HRQoL-14, and CES-D; and satisfaction as measured by surveys. Additionally, response to treatment will be compared with VWF assays and VWF genotype. Our secondary hypotheses will evaluate the safety, tolerability and acceptability of rVWF versus TA as measured by outcomes such as frequency of menorrhagia unresponsive to study drugs or rescue, CS, CL, QoL questionnaires and satisfaction surveys. We hypothesize that rVWF will be as safe, tolerable and acceptable as TA in the

reduction of menorrhagia. Additionally, we hypothesize that VWF assays and VWF genotype will significantly predict response to study treatment.

## 9.2 SAMPLE SIZE DETERMINATION

**Sample Size and Statistical Power:** We propose a phase III multicenter, prospective, randomized crossover trial to compare IV rVWF vs. po TA in reducing menorrhagia in VWD. We powered our trial based on the primary endpoint of a 40-point greater reduction in PBAC when treated with rVWF compared to TA. Assuming intent-to-treat (ITT) analyses, a two-tailed alternative hypothesis with type I error rate of 0.05, a 4-period 2-group (AABB/BBAA) crossover design, an estimated between-subject standard deviation of 63 points and an estimated within-subject standard deviation of 100 points, a total of N=60 patients will provide 84% power to detect a difference in improvement of 40 points or more between rVWF and TA. The sample size was inflated to N=66 to account for an expected dropout rate of 10% or less. Refer to SAP for more details.

Reviewers of the NHLBI 2009 State of the Science (SoS) Hemostasis and Thrombosis panel considered the continuous outcome a limitation and suggested using percent reduction as a more clinically meaningful endpoint. A disadvantage of this approach is that it results in a higher sample size, and, although a dichotomous outcome is clinically relevant, the sample size is too high to achieve in this rare disease.

The difference of 40 points used in our sample size determination was deemed clinically meaningful and feasible, based on six trials in which 95% or more of women receiving rVWF had  $\geq 50\%$  reduction in PBAC (10, 11), and the belief that smaller effects between groups might not change clinical practice or patient behavior, e.g. adopting IV dosing or higher cost treatment.

## 9.3 POPULATIONS FOR ANALYSES

The full analysis set will be based on an intention-to-treat (ITT) analysis, which will comprise all participants who have been randomized to either of the two crossover sequences (AABB/BBAA), regardless of length of follow-up or actual intervention received.

## 9.4 STATISTICAL ANALYSES

### 9.4.1 GENERAL APPROACH

Descriptive statistics will be presented as means and standard deviations for continuous variables and sample proportions for categorical variables. All descriptive statistics will be accompanied by 95% confidence intervals. For inferential tests, a two-tailed p-value  $< 0.05$  (type I error rate of 0.05) will determine statistical significance; the confidence level for confidence intervals will be set at 95%. Covariates and potential remedies to violations of assumptions underlying statistical procedures are specified in the SAP.

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#### 9.4.2 ANALYSIS OF THE PRIMARY EFFICACY ENDPOINT(S)

The primary endpoint is the continuous score on the pictorial blood assessment chart (PBAC), a validated measure of menstrual blood loss described in sections above.

The primary endpoint, PBAC score, will be compared between rVWF and TA using a linear mixed model (LMM) fit via restricted maximum likelihood estimation (REML) to account for repeated measures (65). The distribution of the outcome will be checked for departures from the assumptions of linear mixed modeling, such as normality, and a transformation will be employed as necessary. Treatment and menstrual cycle will be included as fixed effects in the model. Though we expect no crossover effect, we will assess this by testing whether a treatment-by-cycle interaction term is significant. If the interaction is not significant, we will assume no carryover effect and remove the interaction term from the model. Baseline PBAC score will be included as a covariate. The intercept will be allowed to vary randomly to account for subject-level variability of the outcome at baseline. The Kenward-Roger method for calculating degrees of freedom will be used to improve small-sample performance (65). The linear mixed model will allow for unbiased estimates of treatment effects and the utilization of all data under the intention to treat (ITT) principle and the assumption that data are missing at random (MAR). This approach will provide least-squares estimates of the mean reductions in bleeding score on each treatment and allow for statistical comparison of the difference between them. Additional details may be found in the SAP.

As a preventive measure, we will make every attempt to document all reasons for missing data. In addition, baseline characteristics will be compared between participants who do and do not withdraw from the study as a way to assess the impact of missing information and attrition. For missing data from lost or incomplete diaries, HTC nurses will obtain data retrospectively at study visits 1-2 months later, for which recall is excellent. We will investigate the reasons for intermittently missing data (misses an assessment but comes back) and dropouts, and use the likelihood-based procedure if "missing at random" (MAR) is confirmed. If the missing-ness is found to be non-ignorable (missing not at random), we will consider joint or shared parameter models.

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#### 9.4.3 ANALYSIS OF THE SECONDARY ENDPOINT(S)

The secondary endpoints will include continuous and categorical measures described in sections above, such as: a) frequency of menorrhagia unresponsive to study drugs or rescue, recorded by patient diary; b) cycle severity rating (CS); c) cycle length (CL); and d) quality of life questionnaires and satisfaction survey. In addition, response to study treatment will be compared with VWF assays and VWF genotype.

Continuous secondary outcomes, including cycle severity, quality of life, and coagulation measures, will be analyzed with multivariable linear mixed models fit via maximum likelihood using the same approach as for the primary outcome. The same fixed and random effects will be included in secondary outcome models. Multivariable generalized linear mixed models (GLMMs), including the same fixed and random terms as the primary outcome model, will be used to analyze categorical secondary outcomes. Least-

squares estimates of treatment effects will be obtained to determine if significant differences in outcomes exist between rVWF and TA.

#### 9.4.4 SAFETY ANALYSES

**Safety Analyses.** Safety endpoints, including bleeding severity (CS), cycle length (CL), and frequency of menorrhagia unresponsive to study drugs or rescue dose, are secondary endpoints, and will be analyzed as described above. AEs will be coded by “Cancer Therapy Evaluation Program: Common Terminology Criteria for Adverse Events” (CTCAE) (49), calculated (e.g., each AE will be counted once only for a given participant), presented (e.g., severity, frequency, and relationship of AEs to study intervention will be presented by System Organ Class (SOC) and preferred term groupings) and will include for each AE the start date, stop date, severity, relationship, expectedness, outcome, and duration will be analyzed by descriptive statistics, by study subject and study arm, as described above. Safety Stopping Events, below, enumerate specific Adverse events leading to premature discontinuation from the study include:

The **Safety Stopping Events** include:

1. **Uncontrolled Menstrual Bleeding**

Stopping Rules: The DSMB will define stopping of the trial after individual evaluation of uncontrolled menstrual bleeding.

Suspension Rules: A subject develops uncontrolled menstrual bleeding despite or in association with the administration of rVWF or TA, defined as >2 gm% fall in hemoglobin from baseline, and/or requirement for RBC transfusion and/or cardiopulmonary resuscitation.

2. **Thrombosis**

Stopping Rules: The DSMB will define stopping of the trial after individual evaluation of thrombosis.

Suspension Rules: A subject develops severe, catastrophic, or life-threatening thrombosis associated with rVWF or TA, which requires cessation of study drug dosing, with the exception of intravenous (IV) infusion site thrombophlebitis.

3. **Grade 2-5 Allergic Reaction**

Stopping Rules: The DSMB will define stopping of the trial after individual evaluation of a grade 2 or greater allergic reaction.

Suspension Rules: A subject develops anaphylaxis or a grade 2 or greater allergic reaction associated with rVWF or TA, defined by CTCAE grading.

- Grade 2 Intervention or infusion interruption indicated, responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDS, narcotics); prophylactic medications indicated for  $\leq 24$  hours
- Grade 3 Prolonged (e.g. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae (e.g. renal impairment, pulmonary infiltrates)



- Grade 4 Life-threatening consequences, urgent intervention indicated
- Grade 5 Death

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#### 9.4.5 BASELINE DESCRIPTIVE STATISTICS

As described in the SAP, baseline characteristics will be presented using conventional descriptive statistics such as means, standard deviations, counts and proportions. All descriptive statistics will be accompanied by 95% confidence intervals. Baseline comparisons will be performed between the two sequences of treatments (AABB versus BBAA) using two-sample t-tests for interval data, chi-squared tests for categorical variables, or their nonparametric counterparts.

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#### 9.4.6 PLANNED INTERIM ANALYSES

Not applicable.

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#### 9.4.7 SUB-GROUP ANALYSES

Not applicable.

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#### 9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Not applicable.

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#### 9.4.9 EXPLORATORY ANALYSES

**Exploratory Analysis:** This study will have one exploratory analysis, a cost-effectiveness analysis. In this analysis, the primary cost outcome will be menorrhagia treatment costs from the health care sector perspective, i.e., health system costs for implementing each prophylactic treatment and other direct costs associated with menorrhagia care, including medical/surgical costs (all primary, secondary, and tertiary care costs) associated with menorrhagia treatment. We will determine 1) the incremental cost to the health system of implementing the menorrhagia prevention interventions, including medication and infusion costs; and 2) all other menorrhagia care costs not related to the interventions (i.e., all outpatient visits and hospitalizations). The analysis will use costs in 2017 US dollars.

In addition, as a secondary cost outcome, we will determine costs from a societal perspective, which will include the health care sector costs above plus indirect costs resulting from days lost from work or school.

We will collect data pertinent to costs (costs of TA, rVWF, iron infusion, and RBC transfusion; ER/hospital care episodes; days lost from work/school). Intervention and event costs for each intervention will be estimated using Centers for Medicare and Medicaid Services (CMS), Healthcare Cost and Utilization Project (HCUP), and Bureau of Labor Statistics databases. Medication costs will be estimated using average wholesale prices.

The primary effectiveness term will be quality adjusted life years, the product of the quality of life utility value of a health state and the time spent in that state. Utilities measure preferences for health states and range from 0 (death) to 1 (perfect health). Utilities can be derived from a variety of quality of life measures, or measured directly by questionnaires or other techniques. In our analysis, intervention-specific utilities will be derived from SF-36 scores using a validated algorithm. We will calculate 95% CIs around cost and effectiveness estimates and conduct sensitivity analyses to examine the robustness of our assumptions. We will assess intervention program value using incremental cost, incremental effectiveness, and incremental cost effectiveness ratios.

In the primary analysis, differences in healthcare sector costs and effectiveness between interventions will be compared via incremental cost-effectiveness ratios, yielding incremental costs per quality adjusted life year (QALY) gained when comparing one intervention to the other. Secondary analyses will similarly compare societal perspective costs and effectiveness between interventions. In this analysis, work/school absence cost will be calculated by multiplying days absent by the US average daily wages for nonfarm production workers, using US Bureau of Labor Statistics data.

The robustness of cost-effectiveness analysis results will be tested using 1-way sensitivity analyses and probabilistic sensitivity analysis. In 1-way sensitivity analyses, all parameter values will be individually varied to test their effect on cost-effectiveness results. In the probabilistic sensitivity analysis, all model parameters will be simultaneously varied over distributions 5000 times, with results summarized using a cost-effectiveness acceptability curve, which shows the likelihood that interventions are favored over a range of quality adjusted life year dollar value (or acceptability) thresholds, and depict the probability that one strategy is less costly and more effective than the other (i.e., “dominant”). In the US, there is no established cost-effectiveness acceptability criterion; \$50,000-\$150,000 per quality adjusted life year gained is a commonly cited range for justifiable costs based on actual US healthcare spending.

## 10 SUPPORTING DOCUMENTATION AND OPERATIONAL CONSIDERATIONS

### 10.1 REGULATORY, ETHICAL, AND STUDY OVERSIGHT CONSIDERATION

#### 10.1.1 INFORMED CONSENT PROCESS

In obtaining and documenting informed consent, the investigator must comply with applicable regulatory requirements (e.g., 45 CFR Part 46, 21 CFR Part 50, 21 CFR Part 56) and should adhere to ICH GCP. Prior to the beginning of the trial, the investigator should have the IRB’s written approval for the protocol and the written informed consent form(s) and any other written information to be provided to the participants.

##### 10.1.1.1 CONSENT/ASSENT AND OTHER INFORMATIONAL DOCUMENTS PROVIDED TO PARTICIPANTS

Consent forms that describe in detail the study intervention, study procedures, and risks will be given to the study subject. Written documentation of informed consent is required prior to starting or administering a study intervention.

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#### 10.1.1.2 CONSENT PROCEDURES AND DOCUMENTATION

Informed consent is a process that is initiated prior to the individual's agreeing to participate in the study and continues throughout the individual's study participation. Consent forms will be Institutional Review Board (IRB)-approved and the participant will be asked to read and review the document. The investigator will explain the research study to the subject and answer any questions that may arise. A verbal explanation will be provided in terms suited to the subject's comprehension of the purposes, procedures, and potential risks of the study and of their rights as research participants. Subjects will have the opportunity to carefully review the written consent form and ask questions prior to signing. The subjects should have the opportunity to discuss the study with their family or surrogates or think about it prior to agreeing to participate. The subject will sign the informed consent document prior to any procedures being done specifically for the study. Subjects must be informed that participation is voluntary and that they may withdraw from the study at any time, without prejudice. A copy of the informed consent document will be given to study subjects for their records. The informed consent process will be conducted and documented in the source document (including the date), and the form signed, before the participant undergoes any study-specific procedures. The rights and welfare of the subjects will be protected by emphasizing to them that the quality of their medical care will not be adversely affected if they decline to participate in this study.

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#### 10.1.2 STUDY DISCONTINUATION AND CLOSURE

This study may be temporarily suspended or prematurely terminated if there is sufficient reasonable cause. Written notification, documenting the reason for study suspension or termination, will be provided by the suspending or terminating party to study participants, investigator, University of Pittsburgh, participating institutions, and NHLBI. If the study is prematurely terminated or suspended, the Principal Investigator (PI) will promptly inform study participants, the Institutional Review Board (IRB), and sponsor and will provide the reason(s) for the termination or suspension. Study participants will be contacted, as applicable, and be informed of changes to study visit schedule.

Circumstances that may warrant termination or suspension include, but are not limited to:

- Determination of unexpected, significant, or unacceptable risk to participants
- Demonstration of efficacy that would warrant stopping
- Insufficient compliance to protocol requirements
- Data that are not sufficiently complete and/or evaluable
- Determination that the primary endpoint has been met
- Determination of futility

Study may resume once concerns about safety, protocol compliance, and data quality are addressed, and satisfy the sponsor, IRB and/or Food and Drug Administration (FDA).

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### 10.1.3 CONFIDENTIALITY AND PRIVACY

Study participation and related data will be protected to maintain confidentiality. There is a possibility that the subject's personal information or genetic material could 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. In order to reduce risks of disclosure or breach of confidentiality, the research related documents, blood samples and clinical information stored in subject research files will be assigned an alphanumeric (letters and numbers) identifier (that do not contain personal identifiers). For this study, a linkage key for linking this number and the subject's name will be kept at HTC's under lock and key by the principal investigator and research staff. Any publication arising from this study will not contain names or other identification unless study subjects grant permission in another signed consent.

Participant confidentiality and privacy is strictly held in trust by the participating investigators, their staff, and the sponsors and their interventions. This confidentiality is extended to cover testing of biological samples and genetic tests in addition to the clinical information relating to participants. Therefore, the study protocol, documentation, data, and all other information generated will be held in strict confidence. No information concerning the study or the data will be released to any unauthorized third party without prior written approval of the sponsor.

The study monitor, other authorized representatives of the sponsor, representatives of the Institutional Review Board (IRB), regulatory agencies or pharmaceutical company supplying study product may inspect all documents and records required to be maintained by the investigator, including but not limited to, medical records (office, clinic, or hospital) and pharmacy records for the participants in this study, but they will be under the same strict confidentiality requirements. The study participant's contact information will be securely stored at each clinical site for internal use during the study. At the end of the study, all records will continue to be kept in a secure location for as long a period as dictated by the reviewing IRB, Institutional policies, or sponsor requirements.

Study participant research data, which is for purposes of statistical analysis and scientific reporting, will be transmitted to and stored at the University of Pittsburgh Data Coordinating Center. This will not include the participant's contact or identifying information. Rather, individual participants and their research data will be identified by a unique study identification number. The study data entry and study management systems used by clinical sites and by the Data Coordinating Center research staff will be secured and password protected. At the end of the study, all study databases will be de-identified and archived at the CRHC DC Data Coordinating Center.

10.1.4 FUTURE USE OF STORED SPECIMENS AND DATA

Data collected for this study will be analyzed and stored at the University of Pittsburgh Center for Health Care Data Center (CRHC DC) Data Coordinating Center (DCC). After the study is completed, the de-identified, archived data will be transmitted to and stored at the University of Pittsburgh CRHC DC Repository, for use by other researchers including those outside of the study. Permission to transmit data to the University of Pittsburgh CRHC DC Repository will be included in the informed consent.

With the participant’s approval and as approved by local Institutional Review Boards (IRBs), de-identified biological samples will be stored at the University of North Carolina Francis Owen Blood Research Laboratory, Chapel Hill, NC with the same goal as the sharing of data with the University of Pittsburgh CRHC DC Repository. These samples could be used to research the causes of von Willebrand disease and its complications and other conditions for which individuals with congenital bleeding disorders are at increased risk, and to improve treatment. The CRHC DC Data Repository will also be provided with a code-link that will allow linking the biological specimens with the phenotypic data from each participant, maintaining the blinding of the identity of the participant.

During the conduct of the study, an individual participant can choose to withdraw consent to have biological specimens stored for future research. However, withdrawal of consent with regard to bio-sample storage may not be possible after the study is completed. When the study is completed, access to study data will be provided through the University of Pittsburgh CRHC DC Repository and samples will be provided through University of North Carolina Francis Owen Blood Research Laboratory, Chapel Hill.

10.1.5 KEY ROLES AND STUDY GOVERNANCE

**Study Organization and Administration.** The **Clinical Coordinating Center (CCC)** for this multi-site clinical trial will be headquartered at the University of Pittsburgh under the direction of Dr. Ragni, PI. The **Data Coordinating Center (DCC)** for this multi-site clinical trial will be the Clinical Trials and Data Coordinating Center (CCDC), part of the Center for Research on Health Care Data Center (CRHC DC), University of Pittsburgh under the direction of Dr. Doris Rubio, Co-Investigator. Dr. Ragni, an expert in VWD, will direct and be responsible for the scientific and clinical performance of the trial, and regulatory aspects of the trial, including NHLBI and IRB submissions. She will work closely with Dr. Rubio, an expert in statistics and trial design, who will oversee data management and statistical plan and analyses. The CCC and DCC will analyze the data, prepare publications, and jointly monitor the conduct of the study, including recruitment, data quality, and protocol compliance and adherence. The CCC PI and DCC PI will work collaboratively to assure the trial is completed on-time and on-budget. They will meet weekly or biweekly to manage and monitor the trial, review enrollment, assess milestones, identify barriers, and implement strategies and approaches to resolve them in a timely fashion.

Key Roles and Study Governance

Principal Investigator	Medical Monitor
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Margaret V. Ragni, MD, MPH Professor of Medicine and Clinical Translational Science, Department of Medicine	Amy Shapiro, MD Director, Indiana Hemophilia & Thrombosis Center Pediatric Hematology
University of Pittsburgh School of Medicine	Indiana University Health University Hospital
Hemophilia Center of Western PA (HCWP) 3636 Boulevard of the Allies Pittsburgh PA 15213-4306	Indiana Hemophilia & Thrombosis Center, Inc. 8326 Naab Road Indianapolis IN 46260
412-209-7288	317-871-0000
<a href="mailto:ragni@pitt.edu">ragni@pitt.edu</a>	<a href="mailto:ashapiro@ihtc.org">ashapiro@ihtc.org</a>

The CCC PI and DCC PI will serve on and be advised by the **Executive Committee (EC)**, which will also include the NHLBI program officer, Nahed El Kassar, MD, PhD, who will meet monthly to set policy and monitor trial operations, review project-wide issues and formulate policy regarding the conduct of the trial.

The CCC PI and DCC PI will also serve on and be advised by the **Steering Committee (SC)** which will also consist of 10 site HTC MDs rotating staggering 3-year terms, and a Gynecologist Consultant. The SC will set policy, make decisions, and meet quarterly to review and discuss site (HTC) problems and protocol barriers, and monitor and advise on trial progress, as well as safety and efficacy outcomes.

The **Investigator Consortium Network** of approximately 25 HTC MDs and nurse coordinators will participate in monthly conference calls and advise the CCC PI and DCC PI on screening, enrollment, HTC problems and barriers, and clinical and safety problems that arise.

The trial will be monitored by an NHLBI-appointed **Data and Safety Monitoring Board (DSMB)**, including hematologists, statisticians, and clinical trial experts, who will monitor trial progress and safety, review adverse events and severe adverse events and adjudicate safety and efficacy endpoints and study stopping rules.

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#### 10.1.6 SAFETY OVERSIGHT

Safety oversight will be under the direction of a **Data and Safety Monitoring Board (DSMB)** composed of individuals with the appropriate expertise, including experts in hematology, hemostasis, women's health, and statistics. Members of the DSMB should be independent from the study conduct and free of conflict of interest, or measures should be in place to minimize perceived conflict of interest. The DSMB will meet at least semiannually to assess safety and efficacy data on each arm of the study. The DMSB will operate

under the rules of an approved charter that will be written and reviewed at the organizational meeting of the DSMB. At this time, each data element that the DSMB needs to assess will be clearly defined. The DSMB will provide its input to the CCC, DCC, Executive Committee, Steering Committee, and National Institutes of Health staff.

**Data and Safety Monitoring Plan (DSMP).** An external Data and Safety Monitoring Board (DSMB) consisting of members appointed by the National Heart, Lung, and Blood Institute (NHLBI) will monitor the trial, advise the National Institutes of Health (NIH) Program Officer and provide input to the Steering Committee. The DSMB will be composed of nationally recognized experts in hematology, women's health, or in clinical trials. The DSMB will review the study protocol and provide NHLBI with recommendations. Recruitment will be initiated after the NHLBI receives the DSMB recommendation and approves the study protocol. Throughout the course of the trial, the DSMB will review recruitment, retention, data completeness, protocol deviations, adverse events (AEs), severe adverse events (SAEs) and unexpected problems (UPs) on a semi-annual basis and will provide written recommendations to NHLBI.

**Local Data Safety Monitoring Committee.** The local Data Safety Monitoring Committee for this study will include the local PI and Clinical Coordinating Center (CCC) PI, Dr. Ragni, and the nurse coordinator(s), who will meet at least bi-weekly and be responsible for ongoing monitoring all recruitment, data collection and subject confidentiality procedures at this site. Subjects will be closely monitored by the PI, research and clinical staff to ensure subject safety and to ensure that procedures are in place to maintain privacy and confidentiality, progress of study, integrity of the data, procedure reviews and for discussion of pertinent scientific literature or events which could affect the benefit to risk ratio. All serious and unexpected adverse events and/or major breaches of confidentiality will be reported to the sponsor and to the IRB according to regulations outlined in the IRB *Reference Manual for the Use of Human Subjects*. All AE's, SAE's generated from the HTCs will be sent following reporting guidelines to the DCC who will forward to the NIH (see table 9.4.3). A report summarizing the above local and central DSMP activities will be submitted to the IRB at the time of annual renewal.

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### 10.1.7 CLINICAL MONITORING

**Adverse Event Monitoring.** Adverse events will be monitored in four distinct ways: 1) the DSMB will review all reported adverse events and monitor the incidence rates on a semi-annual basis, 2) the expedited review of unexpected SAEs related to the protocol and unanticipated problems (UP), 3) all study outcomes will be evaluated by assigned treatment group on semi-annual basis, and 4) the formal statistical interim monitoring of the efficacy of the primary outcome by assigned treatment group on an annual basis. If unexpected safety concerns arise from the trial data or from external research or literature, then safety data reporting will be expanded and examined on an ad-hoc basis. The Clinical Coordinating Center (CCC) and the Data Coordinating Center (DCC) will work with the NIH and with the DSMB to ensure that the board members have sufficient information to comprehensively monitor patient safety throughout the trial. The DSMB may advise early termination of the trial for safety reasons, efficacy of the primary outcome or other modifications to the protocol.

Because approximately 25 sites across the U.S. will participate in this trial, there will be no on-site monitoring. Instead, monitoring of all records and study subjects will be performed via the University of Pittsburgh CRHC DC electronic database, monthly conference calls with CCC, DCC, and approximately 25 study co-investigators and coordinators, and annual investigator-coordinator study meetings held during the American Society of Hematology annual meeting which most co-investigators attend.

Clinical site monitoring is conducted to ensure that the rights and well-being of trial participants are protected, that the reported trial data are accurate, complete, and verifiable, and that the conduct of the trial is in compliance with the currently approved protocol/amendment(s), with International Conference on Harmonisation Good Clinical Practice (ICH GCP), and with applicable regulatory requirement(s).

The remote monitoring for this study will be performed by The Data Coordinating Center (DCC). The DCC electronic Master Regulatory File (eMRF) will be utilized to remotely monitor the regulatory and study team essential documentation. Each principal investigator will identify a site “registrar” to manage the upload of required information into the eMRF. Please refer to the CCDC Clinical Monitoring Plan (CMP) for additional information related to the eMRF.

*Remote or centralized monitoring will be conducted* prior to all site activation and throughout the study for each study center, the frequency of remote visits will be based on the developed monitoring strategy taking into consideration: enrollment status, data quality, protocol compliance, and the prescribed amount of data to be monitored according to the monitoring plan. Irrespective of other factors, the site will be monitored at least once per year and conducted according to the CCDC CMP (Attachment).

Prior to each remote visit, the DCC will issue a letter notifying the investigator of the scheduled remote audit. The document will be disseminated to the CCC PI, site PI and the study team. The following is a summary of DCC remote audits that will take place:

- **Site Initiation remote visit (SIRV):**
  - The SIRV will be scheduled according to site readiness with regard to institutional approvals and study team availability.
  - The DCC PI, Sr. Administrator and regulatory monitor and CCC National Coordinator will conduct the web-based remote site initiation visit with multiple sites/study teams attending. The presentation will include study team training in the use and application of the eSYS DM specific to the study. A detailed description of topics to be reviewed during the training are outlined in the CCDC CMP.
  - The remote visit will be scheduled in advance. A confirmation letter with meeting agenda will be issued prior to the web teleconference giving notice of the conduct of a remote audit of the eMRF content.
  - Pre-scheduled teleconferences with individual site study teams will take place after the web training. These site-specific teleconferences are designed to discuss eMRF audit findings, discuss site action items and attend to site specific concerns.



- Site Principal Investigator and study team attendance to the SIRV web conference is mandatory. The site PI and his/her lead coordinator are to attend the post SIRV teleconference to discuss site specific concerns.  
**Site Activation Approval-** The DCC will approve site activation once all audit findings confirm site readiness to enroll subjects. The activation of the site will be formalized by the DCC issuance of a site activation letter sent to the CCC and site Principal Investigators.
- **Remote audit of informed consents**
  - The DCC monitor will review the informed consent (IC) document for 100% of subjects enrolled in the study.
  - In the event of amendments during the course of the trial, all subject re-consent will also undergo the 100% consent audit.
  - Study coordinators will upload the IC via the study web portal.
  - A narrative note describing the informed consent process is required for any research study that involves the evaluation of a research intervention (FDA 21 CFR 312.62). This narrative document will undergo DCC audit concurrent with IC review.
- This audit process is described in detail in the CCDC CMP. **Remote audit of study files**
  - 100% of the study files for the first 1-2 subjects enrolled at each study center will be audited at the time of randomization and at study completion.
  - At a minimum, the following data will be monitored:
    - Eligibility, Inclusion/exclusion criteria
    - Source documentation to support diagnosis, inclusion/exclusion criteria
    - Verification protocolized study procedures are completed in keeping with study directives.
    - Review of drug accountability and concomitant medications
    - 100% review of reported SAE
    - Confirmation of PI review and electronic signature on all required eCRF forms.
    - Review of system content to identify errors, omissions, discrepancies
    - Review of study team compliance with DCC-directed action items
  - The process of study subject file audit involves provision of de-identified hard copy upload into the CCDC audit portal. These procedures are described in the CMP training.
  - **eMRF review-** A review of the eMRF will accompany the audit of the 1-2 study subjects at the completion of their study participation to ensure the validity of all regulatory and essential documents.
  - **Audit findings summary report**
    - The DCC monitor will document the audit findings in a summary report within 14 days of the audit and disseminate the report to the CCC and site PI.

All identified action items must be completed within 30 days of the audit report submission date.

○ **For-Cause Remote Audits**

- Remote audits will be conducted if the DCC identifies multiple discrepancies in data entry, delayed response to DCC requested action items, high rate of protocol deviations or site findings that are inconsistent when compared to the performance of other study sites.

The Site PI will be contacted by phone to discuss the concerns and email notification of the date of the for-cause remote audit will be circulated.

○ **Remote Close-out visit**

- Close-out visits may be conducted at study completion or earlier in the case of study termination by the IRB, Data Safety Monitoring Board (DSMB) or FDA.
- A final closeout audit of the eMRF will take place to ensure all regulatory and essential documents are incorporated as expected.

During the course of the study, data checks are completed to ensure no missing data is present. At close out, an audit of all subject data fields will be reviewed, any outstanding data will be identified and requests to complete missing data will be sent to the study team to rectify.

- **Notification of remote audit findings** The Principal Investigators from the CCC and the audited clinical site will be provided copies of monitoring reports within 14 business days of the remote visit(s). Details of clinical site monitoring are documented in a Clinical Monitoring Plan (CMP). The CMP describes the responsibilities of the study team with regard to provision of essential documentation, the process employed by the DCC to conduct the monitoring, the frequency with which the monitoring will be completed, the monitoring to be performed, and the process whereby monitoring reports are disseminated to investigators.

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#### 10.1.8 QUALITY ASSURANCE AND QUALITY CONTROL

Each clinical site will perform internal quality management of study conduct, data and biological specimen collection, documentation and completion. An individualized quality management plan will be developed to describe a site's quality management.

Quality control (QC) procedures will be implemented beginning with the data entry system and data QC checks that will be run on the database will be generated. Any missing data or data anomalies will be communicated to the site(s) for clarification/resolution.

Following written Standard Operating Procedures (SOPs), the monitors will verify that the clinical trial is conducted and data are generated and biological specimens are collected, documented (recorded), and reported in compliance with the protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), and applicable regulatory requirements (e.g., Good Laboratory Practices (GLP), Good Manufacturing Practices (GMP)).

The investigational site will provide direct access to all trial related sites, source data/documents, and reports for the purpose of monitoring and auditing by the sponsor, and inspection by local and regulatory authorities.

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## 10.1.9 DATA HANDLING AND RECORD KEEPING

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### 10.1.9.1 DATA COLLECTION AND MANAGEMENT RESPONSIBILITIES

The Data Coordinating Center (DCC) will oversee all aspects of data management. With the consultation of the DCC, the PI and coordinator will develop an operations manual to standardize all procedures and staff training in areas such as patient recruitment, measurement, assessment, and data entry, management, and security. The DCC coordinator will conduct the initial web-based system training sessions for study teams via online teleconferences. Online access to video training that supports the initial training will be available during the course of the trial. All subsequent training sessions for new study personnel or retraining related to the web-based system or study procedures will be the responsibility of the CCC national coordinator. The DCC will provide consultant support of the CCC coordinator to guide new training sessions and for those study teams that exhibit a need for additional education.

The DCC will create an electronic System for Data Management (eSYS DM), based on detailed study protocols and requirements that includes an electronic case report form and a tracking system, with the capability to incorporate EHR. The eSYS DM is developed using .NET 2.0 to create the interface and SQL for the database. The DCC will work closely with investigative team and other study personnel to ensure that protocols are being followed, data integrity and confidentiality are maintained, and that the data contains a minimum amount of missing data. All study files residing in designated network folders will be backed-up daily and archived weekly. The weekly archived files are maintained for 1 year until the data are erased. All study subjects will be assigned unique study identifiers that will appear on all data collection instruments, electronic media, documents, and files used in the statistical analysis and manuscript preparation. Only authorized team members will have access to personal information needed for tracking and informed consent. Other data quality assurance measures will include detailed documentation of computer operations and data editing procedures and regular meetings with project staff to review any changes in procedure. The DCC also has specific data quality measures that will be implemented. These include data verification, built in data validation mechanisms such as logic and out of range data checks, and repeated evaluation of the data collection and entry process.

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### 10.1.9.2 STUDY RECORDS RETENTION

All records must be maintained for at least seven years. Permission from the Coordinating Center is required prior to record destruction.

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### 10.1.10 PROTOCOL DEVIATIONS

A protocol deviation is any noncompliance with the clinical trial protocol, International Conference on Harmonisation Good Clinical Practice (ICH GCP), or Manual of Procedures (MOP) requirements. The noncompliance may be either on the part of the participant, the investigator, or the study site staff. As a result of deviations, corrective actions are to be developed by the site and implemented promptly.

These practices are consistent with ICH GCP:

- 4.5 Compliance with Protocol, sections 4.5.1, 4.5.2, and 4.5.3
- 5.1 Quality Assurance and Quality Control, section 5.1.1
- 5.2 Noncompliance, sections 5.20.1, and 5.20.2.

It is the responsibility of the site investigator to use continuous vigilance to identify and report deviations within 7 working days of identification of the protocol deviation, or within 7 working days of the scheduled protocol-required activity. All deviations must be addressed in study source documents, reported to the NHLBI Program Officer and the Center for Clinical Trials and Data Coordination. Protocol deviations must be sent to the reviewing Institutional Review Board (IRB) per their policies. The site investigator is responsible for knowing and adhering to the reviewing IRB requirements. Further details about the handling of protocol deviations will be included in the MOP.

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### 10.1.11 PUBLICATION AND DATA SHARING POLICY

The Executive Committee will be responsible for developing publication procedures and resolving authorship issues. The specific grant, U01-A1 HL 133815, is in compliance with:

- The NIH Public Access Policy, the NIH Policy on the Dissemination of NIH-Funded Clinical Trial Information, The Food and Drug Administration Amendments Act of 2007 (FDAAA), Clinical Trials Registration and Results Information Submission rule,
- The NIH Data Sharing Policy

This study will be conducted in accordance with the following publication and data sharing policies and regulations:

National Institutes of Health (NIH) Public Access Policy, which ensures that the public has access to the published results of NIH funded research. It requires scientists to submit final peer-reviewed journal manuscripts that arise from NIH funds to the digital archive [PubMed Central](#) upon acceptance for publication.

This study will comply with the NIH Data Sharing Policy and Policy on the Dissemination of NIH-Funded Clinical Trial Information and the Clinical Trials Registration and Results Information Submission rule. As such, this trial has been registered at ClinicalTrials.gov, NCT02606045, and results information from this

trial will be submitted to ClinicalTrials.gov. In addition, every attempt will be made to publish results in peer-reviewed journals. Researchers will be able to locate and access data and/or other specimens from the VWDMin Trial by formal application which can be found on the BioLINCC website, <https://biolincc.nhlbi.nih.gov>. This repository has data access policies and procedures in place that will provide data access to qualified researchers, consistent with NIH data sharing policies and applicable laws and regulations. Once an investigator application request is approved by NHLBI, and upon receipt of a Research Materials Distribution Agreement, data will be transferred by secure transfers through the BioLINCC website. For biologic specimen requests, upon NHLBI approval of an investigator application request, and with evidence of funding and adequate facilities and expertise to perform the proposed research, BioLINCC will request that the repository prepare and ship the requested biologic specimens.

In addition, this study will comply with the NIH Genomic Data Sharing Policy, which applies to all NIH-funded research that generates large-scale human or non-human genomic data, as well as the use of these data for subsequent research. Large-scale data include genome-wide association studies (GWAS), single nucleotide polymorphisms (SNP) arrays, and genome sequence, transcriptomic, epigenomic, and gene expression data.

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#### 10.1.12 CONFLICT OF INTEREST POLICY

The independence of this study from any actual or perceived influence, such as by the pharmaceutical industry, is critical. Therefore, any actual conflict of interest of persons who have a role in the design, conduct, analysis, publication, or any aspect of this trial will be disclosed and managed. Furthermore, persons who have a perceived conflict of interest will be required to have such conflicts managed in a way that is appropriate to their participation in the design and conduct of this trial. The study leadership in conjunction with NHLBI has established policies and procedures for all study group members to disclose all conflicts of interest and will establish a mechanism for the management of all reported dualities of interest.

### 10.2 ADDITIONAL CONSIDERATIONS

#### 10.2.1 COSTS AND PAYMENTS

**Research Study Costs.** No costs will be incurred by the subject for their participation in this study for research procedures. NIH will compensate HTCs for research procedures as outlined in the contract and budget. IRB preparation costs will be covered, along with research procedures, including screening visits, blood draws for local and central laboratories, blood processing, shipping, lab assays, and HTC charges and services related this study protocol. Pending notification of funding, an NIH-contracted pharmacy will provide rVWF and TA for administration in this study. Research blood draw kits will be prepared by the CRHC DC, according to the linked randomization allocation codes for each study subject, and shipped to each HTC for enrolled subjects.

**Research Study Payments.** Subjects will receive compensation for participation in this study, to help defray the cost of meals, travel, and time lost from work. There will be no additional costs to study

subjects for participation in this study beyond the charges for routine medical care and administration of medications. The study is pending funding by NHLBI. Compensation is based on visits and frequency of blood draws. Subjects will receive \$100 per visit for up to 4 visits during the 24-week trial, including screening visit and 3 study visits, the latter of which includes the end-of-study visit. If subjects do not complete any part of the scheduled study days, compensation for missed visits will not be made. A check will be mailed to each subject upon completion of the study, at least within 4-6 weeks of end of study. If, for whatever reason, subjects complete part but not all of the study, the terms of payment will be determined by the number of visits completed.

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### 10.2.2 HUMAN SUBJECTS

**General Characteristics - Minority Inclusion and Non-Discriminatory Statements.** Females age 13-45 years of age with von Willebrand disease, defined by VWF:RCo <0.50 IU/ml (historic or current), previous bleeding history, and who have menorrhagia and a PBAC >100 in at least one of the two preceding menstrual cycles, and cared for at one of the approximately 25 centers participating in this trial will be eligible for study. It is estimated that up to 60 eligible subjects (inflated to 66 to anticipate dropout) will be enrolled (Table 1). Children under 13 will be excluded as most have not reached regular menses. We shall attempt to recruit subjects in respective proportion to these demographics. All subjects will be screened prior to enrollment for history and laboratory data confirming a VWD diagnosis. Written informed consent will be obtained from all subjects at the screening visit. Once eligibility is confirmed, visit 1 will be defined as start of enrollment. It is estimated that the HCWP site will screen and enroll 2-5 subjects locally, and up to 60 (inflated to 66 to anticipate dropout) nationally. The requirement for PBAC >100 based in at least one of the two preceding menstrual cycles will also serve as baseline menstrual severity for comparison with study drugs.

**Inclusion of Children.** As this study concerns menstrual cycle bleeding, only women, 13-45 years of age will be included. Children under 13 are excluded from participation as most have not reached regular menses.

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### 10.2.3 QUALIFICATIONS

**Qualifications of Investigators.** Dr. Margaret Ragni is a Professor of Medicine, Division Hematology/Oncology, and Director of the Hemophilia Center of Western PA, and has conducted numerous clinical research studies at the University, investigator-initiated and in collaboration with the CDC, FDA, NIH, pharmaceuticals. She is an expert in the area of von Willebrand disease, including pioneer studies of new agents, including rVWF in clinical trials, multicenter genotype phenotype VWD studies, development of better predictors of VWD in children, and developing better therapies for menorrhagia in women with VWD.

Dr. Craig Seaman is an Assistant Professor of Medicine, Division Hematology/Oncology, and Assistant Director of the Hemophilia Center of Western PA. He collaborates with Dr. Ragni on clinical research studies, and is focusing on investigator-initiated studies in hypertension and cardiovascular disease in von Willebrand disease.



## 10.3 ABBREVIATIONS

AE	Adverse Event
CCC	Clinical Coordinating Center
CCDC	Center for Clinical Trials and Data Coordination
CFR	Code of Federal Regulations
CL	Cycle Length
CMP	Clinical Monitoring Plan
CRF	Case Report Form
CRHC DC	Center for Health Care Data Center
CS	Cycle Severity Rating
CTCAE	Common Terminology Criteria for Adverse Events
DCC	Data Coordinating Center
DSMB	Data Safety Monitoring Board
DSMP	Data and Safety Monitoring Plan
eCRF	Electronic Case Report Forms
eSYSDM	Electronic System for Data Management
FDA	Food and Drug Administration
GCP	Good Clinical Practice
GLP	Good Laboratory Practices
GMP	Good Manufacturing Practices
GWAS	Genome-Wide Association Studies
HCWP	Hemophilia Center of Western Pennsylvania
HIPAA	Health Insurance Portability and Accountability Act
HTC	Hemophilia Treatment Center
IB	Investigator's Brochure
ICH	International Conference on Harmonisation
IRB	Institutional Review Board
ITT	Intention-To-Treat
MOP	Manual of Procedures
NCT	National Clinical Trial
NIH	National Institutes of Health
NHLBI	National Heart Blood Lung Institute
OHRP	Office for Human Research Protections
PBAC	Pictorial Blood Assessment Chart
PI	Principal Investigator
QA	Quality Assurance
QC	Quality Control
rVWF	Recombinant Von Willebrand Factor
SAE	Serious Adverse Event
SAP	Statistical Analysis Plan
SOP	Standard Operating Procedure
TA	Tranexamic acid, Lysteda
UP	Unanticipated Problem
US	United States
VNA	Visiting Nurses Association
VWD	Von Willebrand Disease
VWDMin	Von Willebrand Disease Minimize Trial
VWF	Von Willebrand Factor



**10.4 PROTOCOL AMENDMENT HISTORY**

*The table below is intended to capture changes of IRB-approved versions of the protocol, including a description of the change and rationale. A Summary of Changes table for the current amendment is located in the Protocol Title Page.*

<b>Version</b>	<b>Date</b>	<b>Description of Change</b>	<b>Brief Rationale</b>
1.0	03.19.18	Conversion of protocol document to NIH template	NHLBI DSMB reviewed for initial submission
2.0	07.17.18	Amended content for administrative, discrepancy, and formatting corrections; eligibility update	Administrative, discrepancy, formatting corrections; eligibility update for renal disease exclusion
3.0	08.16.19	Inclusion criteria have been relaxed to include age 16-45 and VWD of any type.; and increasing participating sites to approximately 25.	As enrollment is sluggish, there was agreement by NIH and sites to relax inclusion criteria and increase the number of participating sites.
4.0	12.11.19	Inclusion criteria have been relaxed to include age 13-45	Many young girls start on COCs (combined oral contraceptives) and are ineligible for our study. In this study, these young girls have the opportunity to try two new agents for two cycles each, at no cost.
5.0	02.24.20	Exclusion criteria revised to clarify use of hormones (other than progesterone-only), or combined oral contraceptives, and contraceptive implants in past 3 months.	While hormonal contraception has been a contraindication (when using lysteda, and because they increase VWF), progesterone alone contraception does not increase thrombotic risk nor is it a contraindication with Lysteda.

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**VWDMin SAP**  
**February 9, 2018**

**Statistical Analysis Plan**

**Study Design & Objectives.** This a phase III multicenter, prospective, randomized crossover trial that will allocate 60 female patients with type 1 von Willebrand disease (VWD) to either an AABB or BBAA sequence of two treatments to reduce menorrhagia:

- Intravenous Vovendi (rVWF) given on day 1 of menses
- Oral tranexamic acid (TA) given on days 1-5 of menses

All participants will receive one treatment for two menstrual cycles followed by the other treatment for two menstrual cycles.

Our primary hypothesis is that intravenous rVWF will produce a greater reduction in menorrhagia, as measured by the pictorial blood assessment chart (PBAC) score, compared to treatment by oral TA. Specifically, we hypothesize that intravenous rVWF will improve PBAC score by at least 40 points more than TA. Our secondary hypotheses will evaluate the safety, tolerability and acceptability of rVWF versus TA as measured by frequency of menorrhagia unresponsive to study drugs or rescue, cycle severity rating (CSR), cycle length (CL), quality of life questionnaires and satisfaction surveys. We hypothesize that rVWF will be as safe, tolerable and acceptable as TA in the reduction of menorrhagia. Additionally, we hypothesize that VWF assays and VWF genotype will predict response to study treatment as measured by PBAC score.

**Sample Size Calculation.** We powered our trial based on the primary endpoint of a 40-point greater reduction in PBAC when treated with rVWF compared to TA. As rVWF is a greater burden (IV route, cost), rVWF should improve PBAC by 40 points more than TA, a difference the Steering Committee considered clinically significant and sufficient to change practice. In a trial of TA 40% of women had a 50-point reduction in PBAC after 2 cycles, from a baseline PBAC score >100 (1). As rVWF is given intravenously and costs more than TA, the current non-hormonal treatment of choice for menorrhagia, rVWF would need to improve PBAC by 40 points more than TA to be adopted in practice. Thus, a 40-point difference was determined to be the minimal clinically important difference.

Based on data from Byrams on a similar trial in women (2), the between-subject standard deviation was estimated to be 63 points. We conservatively estimated a within-subject standard deviation of 100 points. Assuming intent-to-treat (ITT) analyses, a two-tailed alternative hypothesis with type I error rate of 0.05, and a 4-period 2-group (AABB/BBAA) crossover design, a total of N=60 patients will provide 84% power to detect a difference in improvement of 40 points or more between rVWF and TA. Given an expected dropout rate of 10% or less, where dropout is defined as no follow-up visits after randomization, the sample size was inflated to N=66. NCSS/PASS version 12 software and a repeated measures linear model were used to determine sample size for a superiority parallel arm trial.

**Interim & Final Analyses.** This study will not have any planned interim analyses. The final analyses will be conducted once study follow-up is complete, after all data is cleaned, and once the study database is locked.

**Individual Participant Data.** Individual participant data will not be presented or tabulated.

**Hypotheses.** Our primary hypothesis is that intravenous rVWF can produce an improvement of  $\geq 40$  points more in the pictorial blood assessment chart (PBAC) score than the improvement produced by oral TA. Our secondary hypotheses will evaluate the safety, tolerability and acceptability of rVWF versus TA as measured by frequency of menorrhagia unresponsive to study drugs or rescue, cycle severity rating (CSR), cycle length (CL), quality of life questionnaires and satisfaction surveys.

**Analysis Sets.** The full analysis set will be based on an intention-to-treat (ITT) analysis, which will comprise all participants who have been randomized to either of the two crossover sequences (AABB/BBAA), regardless of length of follow-up or actual intervention received.

**Study Outcomes.** The primary outcome is the score on the pictorial blood assessment chart (PBAC), a valid measure of menstrual blood loss. Secondary outcomes include frequency of menorrhagia unresponsive to study drugs or rescue, cycle severity rating (CSR), cycle length (CL), quality of life measures such as SF-36, RUTA, CDCHRQoL-14, and CESD, and satisfaction as measured by survey.

**Handling of Missing Values.** As a preventive measure, we will make every attempt to document all reasons for missing data. In addition, baseline characteristics will be compared between participants who do and do not withdraw from the study as a way to assess the impact of missing information and attrition.

For missing data from lost or incomplete diaries, HTC nurses will obtain data retrospectively at study visits 1-2 months later, for which recall is excellent (3).

We will investigate the reasons for intermittently missing data (misses an assessment but comes back) and dropouts, and use likelihood-based procedure if "missing at random" (MAR) is confirmed. If the missingness is found to be nonignorable (missing not at random (MNAR)), we will consider joint or shared parameter models.

**Statistical Analyses.** Baseline characteristics including demographics and laboratory measurements will be presented as means and standard deviations for continuous variables and sample proportions for categorical variables. All descriptive statistics will be accompanied by 95% confidence intervals. Baseline comparisons between the two sequences of treatments (AABB versus BBAA) will be performed using two-sample t-tests for continuous variables, chi-squared tests for categorical variables, or their nonparametric counterparts. The distribution of continuous outcomes will be investigated, and transformations to produce normally distributed values (such as natural log) will be employed if the data are skewed.

Assessment of a potential carryover effect: Though evidence suggests that there is no carryover effect from one menstrual cycle to the next when treatments are given for only 1-5 days per cycle, we will test for evidence of a carryover effect in the analysis of each outcome. For each outcome, treatment (rVWF, TA) and period (1-4) will be included as categorical fixed effects, and an interaction between treatment and period will be included. An F-test will be conducted to determine if the interaction term is statistically significant. If the interaction between treatment and period is not significant, then we will remove the interaction from the model and assume that there is no statistically significant carryover effect.

Primary Outcome: The primary endpoint, PBAC score, will be compared between rVWF and TA using a linear mixed model (LMM) fit via restricted maximum likelihood estimation (REML) (4). The natural logarithm of PBAC score will be used as the response variable in the model, as

the distribution of PBAC scores is skewed to the right. Treatment and period will be treated as fixed effects. The chronic conditions of VWD are stable, and the treatments to be tested have only temporary effects. Though evidence suggests that there is no carryover effect from one cycle to the next when treatments are given for only 1-5 days per cycle, we will assess for a carryover effect by including a treatment by period interaction term in the model. If the interaction is not significant, we will assume no carryover effect in statistical analyses and remove the effect from the model. Baseline PBAC score will be treated as a covariate to enhance statistical power and guard against bias due to inadvertent imbalance in baseline scores. The intercept will be allowed to vary randomly to account for subject-level variability of the outcome at baseline. The Kenward-Roger method for calculating degrees of freedom will be used to improve small-sample performance (4). The linear mixed model will allow for unbiased estimates of treatment effects and the utilization of all data under the assumption that data are missing at random (MAR). Least-squares estimates of treatment effects will be obtained on the transformed scale and back-transformed to provide estimated differences by percent change on the original PBAC scale.

Secondary Outcomes: Continuous secondary outcomes, including cycle severity, quality of life, and coagulation measures, will be analyzed with multivariable linear mixed models fit via maximum likelihood using the same approach as for the primary outcome. Multivariable generalized linear mixed models (GLMMs), including the same fixed and random terms as the primary outcome model, will be used to analyze categorical secondary outcomes. Least-squares estimates of treatment effects will be obtained to determine if significant differences in outcomes exist between rVWF and TA.

Subgroup and Exploratory Analyses: This study will not have any planned subgroup or exploratory analyses.

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# Data and Safety Monitoring Plan (DSMP)

Version 1.0  
December 1, 2017

## 1. Introduction

An external Data and Safety Monitoring Board (DSMB) consisting of members appointed by the National Heart, Lung, and Blood Institute (NHLBI) will monitor the trial, advise the National Institutes of Health (NIH) Program Officer and provide input to the Steering Committee. The DSMB will be comprised of experts in hematology, gynecology, women's health, or in clinical trials. The DSMB will review the study protocol and provide NHLBI with recommendations. Recruitment will be initiated after the NHLBI receives the DSMB recommendation and approves the study protocol. Throughout the course of the trial, the DSMB will review recruitment, retention, data completeness, protocol deviations, adverse events (AEs), severe adverse events (SAEs) and unexpected problems (UPs) on a semi-annual basis and will provide written recommendations to NHLBI.

Adverse events will be monitored in four distinct ways: 1) the DSMB will review all reported adverse events and monitor the incidence rates on a semi-annual basis, 2) the expedited review of unexpected SAEs related to the protocol and unanticipated problems (UP), 3) all study outcomes will be evaluated by assigned treatment group on semi-annual basis, and 4) the formal statistical interim monitoring of the efficacy of the primary outcome by assigned treatment group on an annual basis. If unexpected safety concerns arise from the trial data or from external research or literature, then safety data reporting will be expanded and examined on an ad-hoc basis. The Clinical Coordinating Center (CCC) and the Data Coordinating Center (DCC) will work with the NIH and with the DSMB to ensure that the board members have sufficient information to comprehensively monitor patient safety throughout the trial. The DSMB may advise early termination of the trial for safety reasons, efficacy of the primary outcome or other modifications to the protocol.

## 2. DSMB Meeting Materials

Every 6 months, the DSMB will review recruitment, retention, data completeness, protocol deviations and safety data. The CCC and DCC will prepare the materials for the DSMB meetings. Below is an outline of what will be presented at each meeting.

### ***Roster***

Richard C. Becker, MD, Chair  
Veronica Flood, MD, Co-Chair  
Charles S. Abrams, MD  
Susan M. Geyer, PhD  
Robert Glynn, ScD  
Eric F. Grabowski, MD ScD  
Ana S. Iltis, PhD  
Cindy Leissing, MD (Ad Hoc)  
Evan J. Sadler, MD, PhD

### ***Agenda***

#### ***Trial Overview***

**TITLE: U01 Prospective, Randomized, Crossover Trial Comparing Recombinant von Willebrand Factor (*Vonvendi*®, rVWF) with Tranexamic Acid (*Lysteda*®, TA) to Minimize Menorrhagia in Von Willebrand Disease: The VWD Minimize Study**



## Short Title: Von Willebrand Disease Minimize Menorrhagia (VWDMin) Trial

Von Willebrand disease (VWD) is the most common congenital bleeding disorder, occurring in 1% of the population and symptomatic in 0.1%. VWD is caused by defective or deficient von Willebrand factor (VWF), a multimeric protein encoded for on chromosome 12, which results in mucosal bleeding. In women with VWD, menorrhagia is the most common symptom, occurring in 80-90% and associated with iron deficiency, reduced physical and cognitive function, anxiety, depression, and poor quality of life. Current hormonal and non-hormonal therapies are limited by ineffectiveness and intolerance, and few randomized trials are available to guide treatment. The current non-hormonal agent of choice for menorrhagia, tranexamic acid (Lysteda®, TA) is limited by nausea in 50%, and hormonal therapy is ineffective in 30% and poorly tolerated in 20%. Thus, the lack of safe, effective treatment for menorrhagia in women with VWD constitutes a major public health problem.

This is an outpatient, 24-week Phase III prospective, randomized, crossover trial comparing recombinant von Willebrand factor (rVWF) and tranexamic acid (TA, Lysteda®) to minimize menorrhagia in women with type 1 von Willebrand disease (VWD). In this study, women age 18-45 years with mild to moderate VWD and menorrhagia will be enrolled at their hemophilia treatment centers (HTCs) and provide information on menstrual bleeding from their two past monthly cycles to establish baseline bleeding frequency. Only women with regular menses, defined as menses every 21-35 days will be enrolled. A total of 60 subjects (up to 66 for 5% dropout) will be recruited and enrolled at 19 or more HTC sites. Following enrollment, subjects will be randomized to Group I or Group II for up to five days of the next four consecutive menstrual cycles. Those randomized to Group I will be treated with Arm A for menstrual bleeding in cycles 1 and 2, followed by Arm B for menstrual bleeding in cycles 3 and 4. Those randomized to Group II will be treated with Arm B for menstrual bleeding in cycles 1 and 2, followed by Arm A for menstrual bleeding in cycles 3 and 4.

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

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

Subjects randomized to Group I will receive Arm A, rVWF 40 IU/kg intravenously (IV) infusion on day 1 of each of two menstrual cycles, Cycles 1 and 2. They will then be crossed over to Arm B, TA 650 mg 2 tablets orally (po) three times daily on days 1-5 of each of two menstrual cycles, Cycles 3 and 4. Subjects randomized to Group II will receive Arm B, TA 650 mg 2 tablets orally (po) three times daily on days 1-5, for each of two menstrual cycles, Cycles 1 and 2. They will then be crossed over to Arm A, rVWF 40 IU/kg intravenously (IV) infusion on day 1 on each of two menstrual cycles, Cycles 3 and 4. This regimen may be given at the HTC clinic or at home by visiting nurse or patient, if trained. Baseline laboratory studies will be drawn at screening, including *Blood Counts*: hemoglobin, platelets; *Iron Tests*: iron, TIBC, ferritin; *Thyroid Test*: TSH; and *Von Willebrand Tests*: VWF and related tests. Before initiating treatment, subjects will be trained by the HTC nurse on 1) reading urine pregnancy tests and 2) completion of the pictorial blood assessment chart (PBAC), cycle severity score (CSR), and cycle length (CL); and 3) completion of patient diary. Following randomization, subjects will administer home pregnancy tests prior on the first day of each cycle. On each of the four dosing cycles, Cycles 1-4, the PBAC, CSR, and CL will be recorded daily. After completion of study drug in cycle 2, the Crossover Study Visit will occur, during which subjects will be instructed on the new study drug for the study arm to which they will be crossed over; subject diaries will be reviewed and quality of life questionnaires performed. At 10-14 days after completion of study drug in Cycle 4, the End Study Visit will occur, during which subject diaries will be reviewed and returned and quality of life questionnaires performed. All study visits will be within +/- 2 days of the scheduled visit. There are four study visits, at screening, randomization, cross-over (after cycle 2), and end of study (after cycle 4), during which treatment diaries will be reviewed for bleeding frequency, side effects, and medications. Menstrual bleeding by PBAC, cycle severity, cycle duration, and quality-of-life questionnaires, SF-36, Ruta

Menorrhagia Severity Scale, CDC-HRQoL14, and CES-D will be assessed at baseline and after cycle 2 and after cycle 4. A Satisfaction Survey will be completed after 2 cycles of rVWF; and a Cost-Effectiveness questionnaire will be completed after 2 cycles on each treatment, i.e. after cycle 2 and after cycle 4. The study is innovative in the 1) evaluation of recombinant VWF, a new high-purity recombinant VWF protein, to reduce menorrhagia, as compared with the current non-hormonal standard, tranexamic acid (TA); 2) investigation of the relationship of VWF to menstrual bleeding by PBAC score, by assessing VWD parameters: VWF:RCo, VWF:Ag, FVIII:C, VWF multimers, including high molecular weight multimers (HMW) by electrophoresis, and VWF genotype; 3) use of a “home treatment injection” for VWD; 4) comparison of two quality-of-life measures to assess treatment response on each study arm, one specific for bleeding disorders and one specific for menstrual disorders. This trial should have significant impact as lack of effective treatment for menorrhagia is a major unmet need for women with VWD. The University of Pittsburgh will serve as the coordinating center with Dr. Margaret V. Ragni as the Principal Investigator.

#### **Review of DSMB Recommendations**

- *Minutes from previous DSMB Meeting/Call*
- *Response to previous DSMB Meeting/Call*

#### **Progress Report**

- *Progress Report by CCC & DCC*
- *Site Start Dates and Status*
- *Trial Consort Chart*

#### **Patient Enrollment**

- *Screening and Recruitment by Site*
- *Trial Actual Accrual and Targets by Month*

#### **Data Submission**

- *Follow-up Status*
- *Patient Withdrawal*
- *Form Submission*

#### **Enrolled Patient Baseline Characteristics**

- *Baseline Characteristics by Treatment Group*  
Age, severity VWD, usual treatment of heavy menses, H/H, Fe/TIBC/ferritin, TSH  
Pregnancy test, PBAC in most recent two cycles

#### **Protocol Adherence**

- *Protocol Adherence by Treatment Group*  
Group 1: A for 2 cycles, then B for 2 cycles  
Group 2: B for 2 cycles, then A for 2 cycles  
(A=rVWF intravenously day 1 of cycle; B=TA po TID x 5 days of cycle)

#### **DSMB CLOSED BOOK**

##### **Primary Outcome**

- *Primary Outcome by Treatment Group*  
The primary outcome is a 40-point reduction in pictorial blood assessment chart (PBAC) score after two cycles.

### **Study Event Rates**

- Pictorial blood assessment chart (BPAC) Score
- Cycle severity (CS)
- Cycle length (CL)
- Regular and rescue doses (no. doses)
- Allergic reaction
- Heavy bleeding not relieved by study drug
- Thrombosis

### **Patient Event Summaries**

- *Individual Patient Death Summaries*
- *Individual Patient Adverse Event Summaries*
- *Medical Safety Officer Determinations*

### **Interim Analysis of Primary Outcome (Annual Meetings Only)**

#### **3. Definitions of Adverse Events and Unanticipated Problems**

An **adverse event** (AE) is defined as an untoward or unfavorable medical occurrence in a human participant, including any abnormal sign (for example, abnormal physical exam or laboratory finding), symptom, or disease, temporally associated with a person's participation in the research, whether or not considered related to a person's participation in the research.

A **Serious Adverse Event** (SAE) is defined as an adverse event that meets **any** of the following criteria:

- results in death;
- is life-threatening i.e. places a participant at immediate risk of death from the event as it occurred;
- requires inpatient hospitalization or prolongation of existing hospitalization;

*The latter is not regarded as an SAE if:*

- (i) The admission results in a hospital stay of less than 12 hours; OR
- (ii) The admission is pre-planned, i.e. scheduled surgery arranged prior to study; OR
- (iii) The admission is not associated with an AE (e.g. social hospitalization for respite care)

*NB: An invasive procedure during any hospitalization may be reported as an SAE*

- results in a persistent or significant disability/incapacity;
- results in a congenital anomaly/birth defect; OR
- any other adverse event that, based upon appropriate medical judgment, may jeopardize the participant's health and may require medical or surgical intervention to prevent one of the other outcomes listed in this definition.

An **Unanticipated Problem** (UP) is defined as any incident, experience, or outcome that meets **all** of the following criteria:

- Unexpected in terms of nature, severity, or frequency, taking protocol research procedures and participation population characteristics into consideration.
- Related or possibly related to a person's participation in the research.
- Places participants or others at a greater risk of harm (including physical, psychological, economic, or social harm) than was previously known or recognized.

#### 4. Classification of Adverse Events

##### A. Severity

The **severity** of the adverse event refers to the intensity of an event and is categorized as:

- Mild; asymptomatic or mild symptoms; clinical or diagnostic observations only; intervention not indicated,
- Moderate; minimal, local or noninvasive intervention indicated; limiting age-appropriate instrumental activities of daily living,
- Severe or medically significant but not immediately life-threatening; hospitalization or prolongation of hospitalization indicated; disabling; limiting self-care activities of daily living,
- Life-threatening consequences; urgent intervention indicated,
- Death related to AE.

As an alternative, standard grading may be used, e.g. CTCAE, grade 1 to grade 5. If used, a “translation” between the CTCAE system and the standard grading above will be provided.

##### B. Relationship

Relatedness refers to the extent to which an adverse event is considered to be related to the intervention or study procedures. An adverse event is considered **related** if there is a reasonable possibility that the event may have been caused by the procedure. Note that the term “**suspected**” is also means possibly, probably or definitely related to the intervention or study procedures. The following definitions apply to relatedness:

1. Unrelated
  - Adverse event is clearly due to extraneous causes (e.g., underlying disease, environment)
2. Unlikely (adverse event **must meet 2** of the following):
  - Does not have temporal relationship to intervention
  - Could readily have been produced by the participant's clinical state
  - Could have been due to environmental or other interventions
  - Does not follow known pattern of response to intervention
  - Does not reappear or worsen with reintroduction of intervention

3. Possible (adverse event **must meet 2** of the following):
  - Has a reasonable temporal relationship to intervention
  - Could not readily have been produced by the participant's clinical state
  - Could not readily have been due to environmental or other interventions
  - Follows a known pattern of response to intervention
4. Probable (adverse event **must meet 3** of the following):
  - Has a reasonable temporal relationship to intervention
  - Could not readily have been produced by the participant's clinical state or have been due to environmental or other interventions
  - Follows a known pattern of response to intervention
  - Disappears or decreases with reduction in dose or cessation of intervention
5. Definite (adverse event **must meet all 4** of the following):
  - Has a reasonable temporal relationship to intervention
  - Could not readily have been produced by the participant's clinical state or have been due to environmental or other interventions
  - Follows a known pattern of response to intervention
  - Disappears or decreases with reduction in dose or cessation of intervention and recurs with re-exposure

### **C. Expectedness**

An **unexpected** event is one that has not been documented previously as an established adverse reaction to the study intervention and that is not recognized as part of the natural progression of the disease. A particular event may also be considered unexpected if it has a higher severity grade than what has been documented or identified previously.

**Action:** Any action taken while on study drug to resolve the AE is to be documented as follows:

- Drug withdrawn
- Drug interrupted
- Dose not changed
- Dose increased
- Not applicable
- Unknown

**Outcome:** The outcome of the AE is to be documented as follows:

- Not recovered/resolved
- Recovered/resolved
- Recovered with sequelae
- Recovering/resolving
- Fatal
- Unknown

## 5. Data Collection Procedures for Adverse Events

The clinical site staff will report all SAEs on the trial data collection forms. Expected serious adverse events are listed in the manual of operations; these events are recorded on the in-hospital and the 30-day follow-up data collection forms. Site personnel are required to report and document all unexpected SAEs and UPs to the DCC. The DCC will send unexpected SAEs (as reported by the site) to the study Medical Monitor for final assessment of severity, relatedness, and expectedness. The Medical Monitor will remain masked to the treatment strategy while evaluating the SAE.

## 6. Reporting Procedures

**Table: NHLBI Serious Adverse Event and Unanticipated Problems Reporting Timelines**

What Event is Reported	When is Event Reported	By Whom is Event Reported	To Whom is Event Reported
Fatal or life-threatening unexpected, suspected serious adverse reactions	Within <b>24 hours</b> of learning of event.	Investigator	DCC, Local/Internal IRB
	Within <b>72 hours</b> of learning of event.	DCC	NHLBI, DSMB
	Within <b>7 calendar days</b> of learning of event.	DCC	NHLBI, DSMB
Non-fatal, non-life-threatening unexpected, suspected serious adverse reactions	Within <b>15 calendar days</b> of initial receipt of information.	Investigator	DCC, Local/internal IRBs
		Sponsor	FDA, All investigators
Unanticipated adverse device effects	Within <b>10</b> working days of investigator first learning of effect.	Investigator	DCC, Local/internal IRB
		Sponsor	FDA, All investigators
Unanticipated Problem that is not an SAE	Within <b>14 days</b> of the investigator first becoming aware of the problem.	Investigator	DCC, Local/internal IRBs NHLBI, DSMB
All Unanticipated Problems <sup>2</sup>	Within <b>30 days</b> of the IRB's receipt of the report of the UP from the investigator.	IRB	OHRP
		Investigator <sup>3</sup>	External IRBs

<sup>1</sup> Designee is appointed by the sponsor; for example, DCC, CRO.

<sup>2</sup> Per OHRP guidance: only when a particular AE or series of AEs is determined to meet the criteria for an UP should a report of the AE(s) be submitted to the IRB at each institution under the HHS regulations at 45 CFR part 46. Typically, such reports to the IRBs are submitted by investigators.

<sup>3</sup> Investigators should also take into account local IRB guidance if reporting timelines for UPs are shorter than OHRP guidance.

**Reporting Procedures:** All reported SAEs and unanticipated problems will be included in systematic reporting to the DSMB on a semi-annual basis. This includes adverse events and problems previously transmitted through expedited reporting. The following three classes of events will be reported to the NHLBI, the DSMB and the local IRB in an expedited manner: 1) Fatal or life threatening unexpected suspected SAE, 2) Non-fatal, non-life threatening unexpected suspected SAE, and 3) Unanticipated problem. Fatalities related to blood transfusions must be reported to the FDA within 7 days according to guidance: <http://www.fda.gov/BiologicsBloodVaccines/GuidanceComplianceRegulatoryInformation/Guidances/Blood/ucm074947.htm>. Moreover, if a particular SAE is reported with abnormally high frequency during the trial, this will be submitted to the NHLBI Project Officer and the DSMB Executive Secretary for review.

Site personnel will complete and submit an SAE form to the DCC within 24 hours of learning of the event whenever the event is both serious and unexpected. In cases where the event is not serious but places the patient at greater risk of physical, psychological, economic, or social harm, and is both unexpected and related to the study, the site investigator will fill out a UP form within 15 days of learning of the event. SAE forms will be forwarded along with relevant patient history data to the DCC and Medical Monitor for review. The study Medical Monitor will assess the severity, relatedness, and expectedness of the event within 48 hours.

**DCC Reporting for Study Sites:** Following the Medical Monitor's feedback, the DCC will complete an SAE report for adverse events categorized as serious, unexpected and related, and submit the SAE within 72 hours of learning of the event to the NHLBI Project Officer and to the DSMB Executive Secretary. The DCC will also send a final (or updated) report by 7 days of learning of the event. A report for unanticipated problems will also be sent by the DCC to the NHLBI Project Officer and the DSMB Executive Secretary for review. The DCC will send the reports to the NHLBI DSMB Executive Secretary and the NHLBI Medical Monitor for review. All reporting from the time that the Site learns about the event until it is reported to the NHLBI, DSMB, FDA and IRBs will follow the NHLBI DSMB established timelines as specified in <https://www.nhlbi.nih.gov/research/funding/human-subjects/adverse-event>) as shown above. Upon receipt of an expedited report, the DSMB chair will decide whether the event should be discussed at the next scheduled DSMB meeting or discussed as soon as possible at an ad-hoc meeting.

**Reporting of Local IRB Actions.** IRB actions regarding the trial will be communicated to the NHLBI Project Officer and NHLBI Executive Secretary in an expedited fashion. If the IRB or ethics board at any site, CCC or DCC takes action regarding the trial (e.g., the IRB places a hold on the trial or suspends the trial), the site will report this to the CCC within 24 hours of the action. The Site will submit written documentation from the IRB, an explanation of the circumstances, and a plan of action to the CCC within 72 hours. The CCC will promptly communicate this information to the DCC, and the DCC, will be responsible for notifying the NHLBI Project Officer and the DSMB Executive Secretary. A written report describing the IRB decision, the rationale for the decision, and the plan of action based on this decision will be submitted to the NHLBI Project Officer and the DSMB Executive Secretary within 7 days of the IRB action.

## 7. Adverse Event Reporting Period

All randomized patients will be followed for 24 weeks. Reporting of AEs will cease at the conclusion of the trial.

### A. The Recruitment and Statistical Interim Monitoring Time Schedule

The enrollment goal is 60 subjects (66 for up to 5% dropouts). The proposed accrual timeline is below.

#### Milestone Accrual Timeline

	Proposed Target Accrual	Proposed Cumulative Accrual	% Study Completion Information
8/15/17	0	0	0%
11/15/17	0	0	0%
2/15/18	0	0	0%
5/15/18	0	0	0%
8/15/18	2	2	3.3%
11/15/18	2	4	6.1%
2/15/19	2	6	9.1%
5/15/19	4	10	15.1%
8/15/19	4	14	21.2%
11/15/19	4	18	27.3%
2/15/20	4	22	33.3%
5/15/20	4	26	39.4%
8/15/20	6	32	48.5%
11/15/20	6	38	57.6%
2/15/21	6	44	66.7%
5/15/21	6	50	75.7%
8/15/21	8	58	87.9%
11/15/21	8	66	100.0%
2/15/22	0	66	100.0%
5/15/22	0	66	100.0%
8/15/22	0	66	100.0%



## **B. Statistical Interim Monitoring: Boundary Curves**

NA

## **C. Considerations for Stopping the Trial**

We will allow the trial to run to completion if the intervention appears at least as effective as standard TA therapy. We propose halting the trial if a safety event reaches any stopping rules: (i) uncontrolled menstrual bleeding; (ii) thrombosis; or (iii) or grade 2-5 allergic reactions. The DSMB will review each event to determine if the trial should be halted. Statistical interim monitoring results should be taken as one component to the decision as to whether or not to stop a trial. To stop the trial for efficacy, results should be definitive enough to be able to change clinical practice. The DSMB will use the monitoring information to determine its recommendation to NHLBI. The DSMB can recommend that the trial should continue as proposed, that the protocol should be modified based on the results seen in one treatment comparison or in some well-defined subgroup of patients, or that the trial should be terminated early. The final decision to stop trial rests with the NHLBI. If recommendation is to stop the trial, the trial principal investigators shall be consulted before a final decision is made.

## **Suspension and Stopping Rules**

According to the protocol Safety Stopping Rules, the trial will be terminated if an event(s) reach any stopping rules. A terminated trial means no further subjects are enrolled or treated. If an event(s) trigger any suspension rules, the study will put on hold until the DSMC and Medical Monitor evaluate the event and make a final recommendation. A suspended trial means no further subjects are enrolled, but already enrolled subjects will be treated. In addition, all subjects who develop inhibitors, no matter the treatment they receive, will be monitored.

The **Safety Stopping Events** include:

### **1. Uncontrolled Menstrual Bleeding**

Stopping Rules: The DSMB will define stopping of the trial after individual evaluation of uncontrolled menstrual bleeding.

Suspension Rules: A subject has uncontrolled menstrual bleeding despite or in association with the administration of rVWF or TA.

### **2. Thrombosis**

Stopping Rules: The DSMB will define stopping of the trial after individual evaluation of thrombosis.

Suspension Rules: A subject develops severe, catastrophic, or life-threatening thrombosis associated with rVWF or TA, which requires cessation of study drug dosing, with the exception of intravenous (IV) infusion site thrombophlebitis.

### 3. **Grade 2-5 Allergic Reaction**

Stopping Rules: The DSMB will define stopping of the trial after individual evaluation of a grade 2 or greater allergic reaction.

Suspension Rules: A subject develops anaphylaxis or a grade 2 or greater allergic reaction associated with rVWF or TA, defined by CTCAE grading.

- Grade 2 Intervention or infusion interruption indicated, responds promptly to symptomatic treatment (e.g. antihistamines, NSAIDS, narcotics); prophylactic medications indicated for  $\leq 24$  hours
- Grade 3 Prolonged (e.g. not rapidly responsive to symptomatic medication and/or brief interruption of infusion); recurrence of symptoms following initial improvement, hospitalization indicated for clinical sequelae (e.g. renal impairment, pulmonary infiltrates)
- Grade 4 Life-threatening consequences, urgent intervention indicated
- Grade 5 Death

## **Appendix: Conditional Power Calculations**

At the request of the Data Safety and Monitoring Board on January 26, 2022, the Data Coordinating Center (DCC) has conducted conditional power calculations for the Von Willebrand Disease Minimize Menorrhagia (VWDMin) Trial, using all data collected to date in the trial (N=36 participants with any post-baseline PBAC scores).

**Such calculations were carried out assuming:**

**(A) original baseline assumptions regarding variability in PBAC scores as stated in the Statistical Analysis Plan (SAP)**

**(B) updated variability estimates in PBAC scores as observed in the trial.**

For each set of variability assumptions, conditional power was estimated for N=50, N=55, and N=60 total participants via simulation with K=10,000 iterations per scenario. Observed data from the N=36 participants with any post-baseline PBAC scores to date were utilized, and additional patient PBAC scores (for N=14, N=19, and N=24 additional patients) were simulated under each set of assumptions.

For each simulation iteration, the primary endpoint, PBAC score, was compared between rVWF and TA using a linear mixed model (LMM) fit via restricted maximum likelihood estimation (REML) with the Kenward-Roger method for calculating degrees of freedom. The natural logarithm of PBAC score was used as the response variable in the model, as specified in the SAP. The model included treatment (rVWF, TA) and cycle (1, 2, 3, 4) as categorical fixed effects, and a random subject effect (i.e., random intercept) was included to account for between-subject variability in the outcome. When the coefficient for the treatment variable produced a p-value<0.05 and the coefficient for treatment was negative (in other words, in the direction of greater reduction in PBAC when on rVWF compared to TA), the simulated trial was considered a “success.” The proportion of all K=10,000 iterations that were declared a “success” served as our conditional power estimate for a given set of assumptions.

Details regarding the data generating process for simulated participants are provided below under (A) the original baseline assumptions and (B) updated variability assumptions.

**(A) Original baseline assumptions as stated in the SAP:**

**1. A between-subject standard deviation of 63 points on the raw PBAC scale.**

**2. A within-subject standard deviation of 100 points on the raw PBAC scale.**

Additionally, a difference in mean PBAC scores of -40 points between rVWF cycles and TA cycles was assumed, as this is the minimal clinically important difference to detect. PBAC scores for simulated patients were randomly sampled from a multivariate (4-dimensional) Normal distribution with exchangeable covariance structure assuming the aforementioned parameters.

Note: as the natural log of PBAC scores was pre-specified as the response variable in the analysis of the primary endpoint, if a simulated PBAC score was less than 1, the value was set to equal 1 (so as to avoid a log-transformed value of negative infinity, which would result in an unreliable model fit).

Results of the conditional power calculations under (A) are given below:

Total Sample Size	Number of Iterations (out of 10,000) resulting in trial success	Conditional Power
N=50 (14 simulated patients)	0	0.00%
N=55 (19 simulated patients)	0	0.00%
N=60 (24 simulated patients)	0	0.00%

**(B) Updated variability estimates in PBAC scores as observed in the trial to date:**

Based on data for N=36 participants with any post-baseline PBAC scores to date in the trial, the sample variability in baseline PBAC scores was partitioned into between-subject variability and within-subject variability. The observed variability in PBAC scores differed substantially from the baseline assumptions used in the original sample size calculation (both within- and between-subject). We performed a second set of conditional power calculations using the following updated variability assumptions:

1. A between-subject standard deviation of 314.01 points on the raw PBAC scale.
2. A within-subject standard deviation of 150.15 points on the raw PBAC scale.

A difference in mean PBAC scores of -40 points between rVWF cycles and TA cycles was still assumed, as this is the minimal clinically important difference to detect. PBAC scores for simulated patients were randomly sampled from a multivariate (4-dimensional) Normal distribution with exchangeable covariance structure assuming the aforementioned parameters.

Note: as the natural log of PBAC scores was pre-specified as the response variable in the analysis of the primary endpoint, if a simulated PBAC score was less than 1, the value was set to equal 1 (so as to avoid a log-transformed value of negative infinity, which would result in an unreliable model fit).

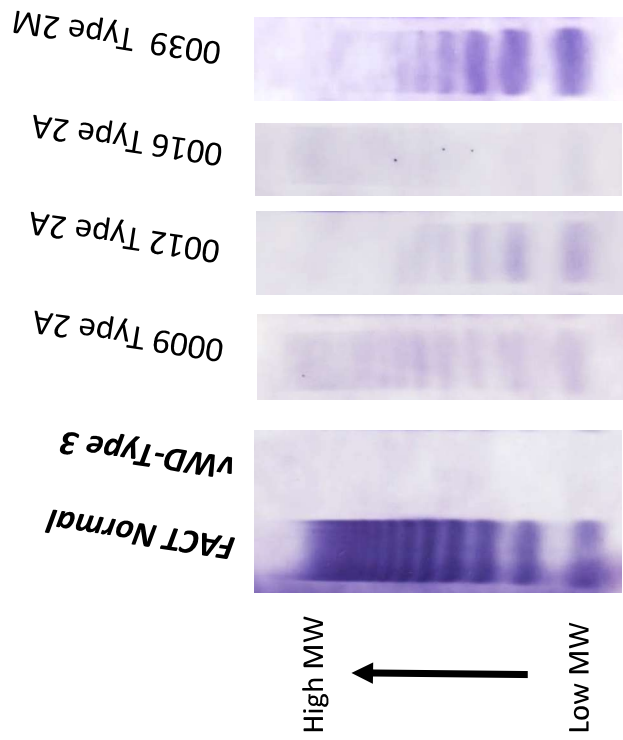
Results of the conditional power calculations under (B) are given below:

Total Sample Size	Number of Iterations (out of 10,000) resulting in trial success	Conditional Power
N=50 (14 simulated patients)	0	0.00%
N=55 (19 simulated patients)	0	0.00%
N=60 (24 simulated patients)	0	0.00%

**In summary, the conditional power assuming (A) original baseline assumptions as stated in the SAP was estimated to be 0.00% when the total sample size equals N=50, 55, and 60 participants. The conditional power assuming (B) updated variability estimates as observed in the trial was estimated to be 0.00% when the sample size equals N=50, 55, and 60 participants.**

All simulations and calculations were performed using R version 3.6.3.

VWF Multimers – VWDMin Type 2 Subjects



**Table 4. Cost Analysis of TA vs. rVWF in Reducing HMB**

**I. DRUG COSTS**

	<b>Cost<sup>1</sup></b>	<b>Unit Cost</b>	<b>Dose</b>	<b>Total Cost Per Patient</b>
<b>Recombinant VWF (rVWF) N=17</b>			@40 IU/kg/60kg	Not including infusion cost
500 IU	\$287.83	\$0.576	2400 IU	\$1,381.58
1000 IU	\$453.74	\$0.454	2400 IU	\$1,088.98
<b>Tranexamic Acid (TA) N=19</b>			@30/5 days	Drug cost only
650 mg	\$14.87	\$0.496	30 tabs	\$14.87

**II. OTHER COSTS**

**Emergency Department Visit**

<b>HCPCS Code</b>	<b>Cost<sup>2</sup></b>	<b>Total Cost Per Patient<sup>4</sup></b>
Moderate-high (99284)	\$123.20	\$21.74

<b>Lost Income</b>	<b>Cost<sup>3</sup></b>	<b>Missed Day Cost Per Patient<sup>5</sup></b>
Average hourly wage Total private non-farm June 2022	\$32.11	\$256.88

<sup>1</sup> Federal Supply Schedule, <https://www.va.gov/opa/nac/fss/pharmPrices.asp>

<sup>2</sup> CMS Physician Fee Schedule, <https://www.cms.gov/medicare/physicians-fee-schedule/search/overview>

<sup>3</sup> Bureau of Labor Statistics, <https://www.bls.gov/news.release/empsit.t19.htm>

<sup>4</sup> This was based on three emergency department visits associated with TA treatment in 36 patients.

<sup>5</sup> This was based on one additional missed day of work on average associated with TA treatment.

**Table 5. VWF Next Gen Sequencing and Bleeding Severity**

Variants*	Subjects	VWF:Ag**	PBAC Score***				
		Baseline	Baseline		After TA	After rVWF	rVWF – TA Treatment Effect
	No.	Mean ± SD	Mean ± SD	Mean (95% CI)	Mean ± SD	Mean ± SD	Adj Mean Diff (95% CI)
Pathogenic/Likely Pathogenic (P/LP)	8	0.24 ± .14	490 ± 225	490 (249, 731)	208 ± 149	216 ± 209	10 (-92, 112)
Variants of Uncertain Significance (VUS)	6	0.45 ± .14	570 ± 389	570 (291, 848)	228 ± 261	316 ± 371	66 (-94, 226)
Nonpathogenic/None (NP/N)	22	0.41 ± 0.14	545 ± 374	545 (399, 691)	231 ± 213	281 ± 172	51 (-4, 105)

Variants are named using VWF transcript NM\_000552.

\***Pathogenic variants** included 5 nonsynonymous variants in 5 subjects: c.421G>A (p.Asp141Asn); c.4121G>T (p.Arg1374Leu); c.4517C>T (p.Ser1506Leu); c.3797C>T (p.Pro1266Leu); and c.311\_312del (p.Gln104Argfs\*19).

\***Likely pathogenic variants** included 2 nonsynonymous variants in 3 subjects: c.4751A>G (p.Tyr1584Cys) and c.648-3C>A.

\***Variants of uncertain significance** included 8 nonsynonymous variants in 6 subjects: c.4130C>T (p.Ala1377Val); c.1730-10C>A; c.3692A>C (p.Asn1231Thr); c.3686T>G (p.Val1229Gly); c.4697G>A (p.Arg1566Gln); c.3827T>G (p.Leu1276Arg); c.1325G>A (p.Arg442His) ex12; c.5171-9del.

\*\*Mean and standard deviation (SD) for baseline VWF:Ag level were compared using two-sample t-test.

p=0.017, comparing VWF:Ag between P/LP and VUS.

p=0.007, comparing VWF:Ag between P/LP and NP/N.

p=0.531, comparing VWF:Ag between VUS and NP/N.

\*\*\*Mean and 95% CI for baseline PBAC score were estimated using linear mixed effects models with a random intercept for participant. Adjusted mean difference and 95% CI for treatment effect were estimated using linear mixed-effects models including fixed effects for treatment, menstrual cycle, baseline score, and random intercept for participant.

## VWD Min Trial Enrollment Table

Site	PI	Subjects Screened	Subjects Enrolled	Subjects Completed Study
University of Pittsburgh, PA, Pittsburgh PA	Margaret V. Ragni MD	N=13	N=11	N=11
Banner MD Anderson Cancer Center, Gilbert AZ	Danielle Nance, MD	N=6	N=6	N=5
University of California, San Francisco	Andrew D. Leavitt MD	N=4	N=4	N=3
Versiti Blood Research Institute, Milwaukee WI	Lynn Malec, MD	N=3	N=3	N=3
Michigan State University, East Lansing MI	Roshni Kulkarni, MD	N=3	N=2	N=2
Emory University, Atlanta GA	Robert Sidonio, MD	N=3	N=2	N=2
Ohio State University, Columbus OH	Eric Kraut, MD	N=2	N=2	N=2
Cure 4 the Kids, Las Vegas NV	Joseph Lasky, MD	N=3	N=2	N=2
Mayo Clinic, Rochester MN	Rajiv Pruthi, MBBS	N=3	N=2	N=2
Cleveland Clinic, Cleveland OH	Dana Angelini, MD	N=2	N=2	N=1
Rutgers University, New Brunswick NJ	Claire Philipp, MD	N=1	N=1	N=1
Center Inherited Bleeding Disorders, Orange CA	Nina Hwang, MD	N=1	N=1	N=1
Vanderbilt University, Nashville TN	Allison P. Wheeler, MD	N=1	N=1	N=1