Intervention:

Recombinant von Willebrand factor (rVWF, Vonvendi®) 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.

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

- **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 19 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 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 19 participating HTCs indicated agreement on our approach to compare rVWF with TA, and with use 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 tables 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. Adult females 18-45 years of age.
2. Mild or moderate type 1 von Willebrand disease (VWF:RCo <0.50 IU/ml, normal multimers, 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 or oral contraceptives or contraceptive implant 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.

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.

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 type 1 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

>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 (CSR) and Cycle Length (CL).** The cycle severity (CS) and cycle duration (CSL) 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 rWF 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.

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. 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 **<u>any</u>** 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

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

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) v 4.03, June 14, 2010 (50). 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 **24 hours** of event.	Investigator	DCC, Local/Internal IRB
	Within **72 hours** of event.	DCC	NHLBI, DSMB
	Within 7 calendar days of event	DCC	NHLBI, DSMB
Non-fatal, non-life-threatening unexpected, suspected serious adverse reactions	Within **15 calendar days** of initial receipt of information	Investigator	DCC, Local/internal IRBs
		Sponsor	FDA, All investigators
Unanticipated Problem that is not an SAE	Within **14 days** of the investigator becoming aware of the problem	Investigator	DCC, Local/internal IRBs NHLBI, DSMB
All Unanticipated Problems[2]	Within **30 days** of the IRB's receipt of the report of the UP from the investigator.	IRB	OHRP
		Investigator[3]	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

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.

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 (CSR); 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 (CSR), 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) v 4.03, June 14, 2010 (50), 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 ≤ 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

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.

9.4.6 PLANNED INTERIM ANALYSES

Not applicable.

9.4.7 SUB-GROUP ANALYSES

Not applicable.

9.4.8 TABULATION OF INDIVIDUAL PARTICIPANT DATA

Not applicable.

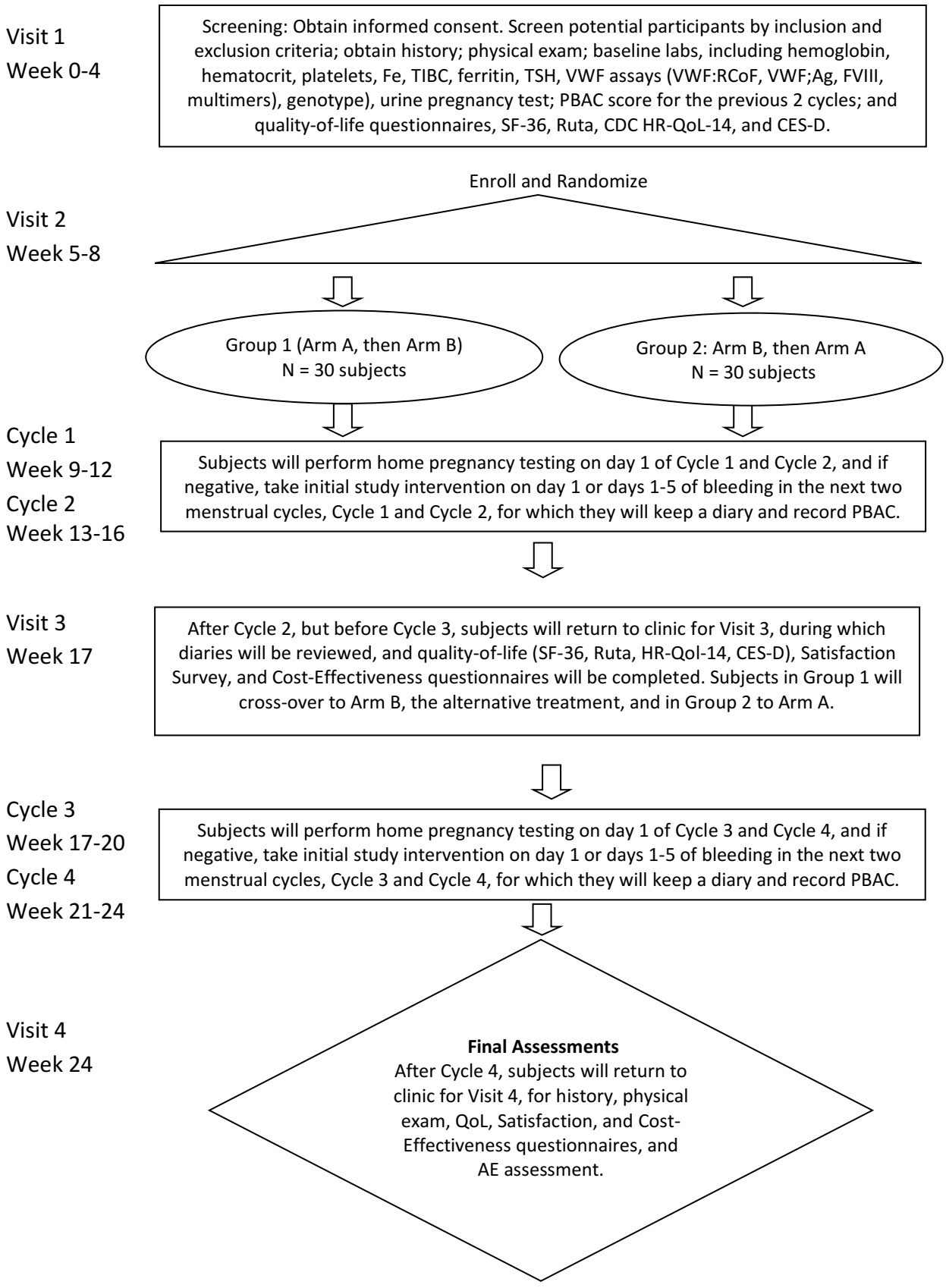
9.4.9 EXPLORATORY ANALYSES

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.

Version	Date	Description of Change	Brief Rationale

1.2 SCHEMA


Visit 1
Week 0-4
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.
Enroll and Randomize
Visit 2
Week 5-8
Group 1 (Arm A, then Arm B)
N = 30 subjects
Group 2: Arm B, then Arm A
N = 30 subjects
Cycle 1
Week 9-12
Cycle 2
Week 13-16
Subjects will perform home pregnancy testing on day 1 of Cycle 1 and Cycle 2, and if negative, take initial study intervention on day 1 or days 1-5 of bleeding in the next two menstrual cycles, Cycle 1 and Cycle 2, for which they will keep a diary and record PBAC.
Visit 3
Week 17
After Cycle 2, but before Cycle 3, subjects will return to clinic for Visit 3, during which diaries will be reviewed, and quality-of-life (SF-36, Ruta, HR-QoI-14, CES-D), Satisfaction Survey, and Cost-Effectiveness questionnaires will be completed. Subjects in Group 1 will cross-over to Arm B, the alternative treatment, and in Group 2 to Arm A.
Cycle 3
Week 17-20
Cycle 4
Week 21-24
Subjects will perform home pregnancy testing on day 1 of Cycle 3 and Cycle 4, and if negative, take initial study intervention on day 1 or days 1-5 of bleeding in the next two menstrual cycles, Cycle 3 and Cycle 4, for which they will keep a diary and record PBAC.
Visit 4
Week 24
Final Assessments
After Cycle 4, subjects will return to clinic for Visit 4, for history, physical exam, QoL, Satisfaction, and Cost-Effectiveness questionnaires, and AE assessment.

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 strong 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

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: Adult females with mild or moderate type 1 VWD, age 18-45 years, defined by VWF:RCo < 0.50 IU/mL, normal VWF multimers, 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 19 HTCs participating in this trial w*ill be eligible for study.* Subjects approached for participation in this study will have type 1 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

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

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 score (CSR), 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 FOBRL 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

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. The Medical Monitor will remain masked to the transfusion strategy while evaluating the SAE.

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

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 Score (CSR), 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, CSR, 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 type 1 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.

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.

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