IRB Approved
Document Release Date: 12/27/2017

FRED HUTCHINSON CANCER RESEARCH CENTER
UNIVERSITY OF WASHINGTON SCHOOL OF MEDICINE

Current version: 3
Previous version:2

Management of Venous Thromboembolic Events (VTE) in Patients with Hematologic Disorders and Treatment-Induced Thrombocytopenia: a Pilot Study

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PROTOCOL SYNOPSIS

Protocol Title	Management of Venous Thromboembolic Events (VTE) in Patients with Hematologic Disorders and Treatment-Induced Thrombocytopenia: a Pilot Study
Protocol Number	
Protocol Sponsor	None
Trial Phase	Pilot
Trial Type	Noninferiority
Clinical Indication	Management of treatment-induced thrombocytopenia during anticoagulation
Study Objectives	1) Determine feasibility of an RCT comparing platelet transfusion thresholds of 30 $x10^9$ vs 50 $x10^9$ in anticoagulated patients 2) Report bleeding outcomes as they would be in a full trial 3) Report patient reported outcomes as they would be in a full trial
Study Design	Randomized controlled trial
Population	Adult patients with moderate to severe thrombocytopenia related to the treatment of a hematologic malignancy and/or stem cell transplant for a hematologic disorder who require anticoagulation for a recently diagnosed venous thrombosis.
Primary Endpoints	(1) Feasibility defined as ≥12 patients enrolled over a 1-year period and (2) ≥70% compliance with study-determined transfusion threshold at the time of count recovery
Secondary Endpoints	(1) Number of eligible patients over a 1-year period (2) Percentage of eligible patients providing consent (3) Progressive or new venous or arterial thrombosis (4) Bleeding events by WHO grade (5) Platelet transfusions (6) PRBC transfusions (7) Transfusion related outcomes (8) Quality of life (FACT-Th18)
Type of control	Institutional standard of care
Trial Blinding	Unblinded
Treatment Groups	A: transfusion threshold of $30x10^9$/L B: transfusion threshold of $50x10^9$/L
Treatment Schedule	Transfusions will be administered as needed (based upon randomized threshold) throughout a single period of treatment-related thrombocytopenia OR 30 days, whichever is shorter
Number of trial subjects	12
Estimated duration of trial	One year
Duration of Participation	≤ 63 days

ABBREVIATIONS

CT scan	Computed tomography scan
ATE	Arterial thromboembolism
HSCT	Hematopoietic Stem Cell Transplant
SCCA	Seattle Cancer Care Alliance
VTE	Venous thromboembolism
AML	Acute myeloid leukemia
ALL	Acute lymphocytic leukemia
CML	Chronic myeloid leukemia
CLL	Chronic lymphocytic leukemia
MDS	Myelodysplastic syndrome
WHO	World Health Organization
DIC	Disseminated intravascular coagulation
PT	Prothrombin time
PTT	Partial thromboplastin time
V/Q	Ventilation/perfusion scan
APL	Acute promyelocytic leukemia
HLA	Human leukocyte antigen

Contents

1.0 GENERAL INFORMATION

1.1 Protocol Title

"Management of Venous Thromboembolic Events (VTE) in Patients with Hematologic Disorders and Treatment-Induced Thrombocytopenia: a Pilot Study."

1.2 Sponsor Information

This is a pilot study and will not be sponsored.

1.3 Investigator Information

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2.0 INTRODUCTION TO THE PROTOCOL

This document provides in depth background information and serves as a guidance document for the proper identification, treatment and maintenance of trial patients. This study will be conducted in compliance with the IRB approved protocol, associated Federal regulations and all applicable IRB requirements. The purpose of this study is to evaluate the feasibility of a randomized, controlled trial comparing a platelet transfusion threshold of $30x10^9$/L to $50x10^9$/L in anticoagulated patients with treatment related thrombocytopenia. To date no clinical trial has ever investigated the safety and efficacy of any transfusion strategy in this setting. This will be a pilot study in which approximately 12 patients will be enrolled and randomized to one of the two potential transfusion thresholds. Patients will be followed clinically for bleeding, thrombotic and transfusion related outcomes.

2.1 Background and Rationale

Venous thromboembolic disease (VTE) is a common complication of hematologic malignancy. The prolonged periods of thrombocytopenia experienced by these patients during curative-intent chemotherapy and/or hematopoietic stem cell transplant (HSCT) do not appear to provide protection against VTE: the rate of symptomatic VTE may be as high as 5% by day 180 post HSCT.[1] Data to guide management of thrombosis in these patients, particularly during periods of moderate to severe thrombocytopenia, are sparse.

The International Society on Thrombosis and Haemostasis (ISTH) has suggested an empirical cut-off of $50x10^9$/L as the minimum platelet threshold above which therapeutic anticoagulation is considered to be safe. Accordingly, a recommendation has been made to consider platelet

transfusion support to maintain a platelet count above this threshold if therapeutic anticoagulation is warranted, as in the setting of acute VTE.[2] These recommendations, however, have been made on the basis of expert consensus, as there is no high-quality evidence.

The only data currently available in the literature comes from very small retrospective studies and case series. These suggest the risk of bleeding (WHO grade 2 or greater) among patients with moderate to severe thrombocytopenia is relatively low (between 7.7 and 9.4% over a 3-6 month period) when patients are initiated on anticoagulation and then transfused toward a goal of 40-50x10^9/L.[3,4] Approximately half of these bleeding episodes represent major bleeding (3.8% of patients).[4]

2.2 Clinical Data to Date

A recent survey of malignant/nonmalignant hematologists and transfusion medicine experts about this topic found a marked degree of variation in proposed transfusion thresholds (ranging from 25 to 50x10^9/L).[5] A recent retrospective study of eighty-two SCCA patients with VTE during a period of treatment-related thrombocytopenia demonstrated that most providers here manage VTE with therapeutic anticoagulation, adjusting the platelet transfusion goal to 50 x10^9/L, often resulting in two or more weeks of frequent platelet transfusions, potentially repeated in future treatment cycles. Bleeding rates (WHO grade 2 or above) were noted to be somewhat higher than those previously reported in the literature (37% at 30 days), but comparable to or less than rates expected in patients with severe treatment related thrombocytopenia (transfusion threshold 10x10^9/L), which is as high as 70% over a period of 30 days or less.[6] While retrospective assessments of bleeding, particularly grade 2 bleeds, are limited and some bleeds are likely missed by this method, we expect this rate of bleeding is more representative of actual outcomes than those previously reported in the literature.

Our retrospective review demonstrated that the vast majority of patients at our institution in this situation are transfused to maintain a platelet count ≥ 50x10^9/L, with the above noted bleeding rate. The majority of bleeds occurred during a time when the platelet count was at or above this goal (mean 52 x10^9/L) although the retrospective nature made it impossible to define or compare 'at risk' times. We did, however, note a number of transfusion related complications with this strategy including transfusion reactions in 13% of patients and volume overload requiring diuretic therapy or dialysis in 37% of patients.

Patients received a median of 6 transfusions over the 30 days following diagnosis, accompanied by both a financial cost and a drain on resources. While cost data were not collected as a part of this study, previous studies have demonstrated increased cost (as high as $5700/patient in 2014) associated with the use of prophylactic platelet transfusions to target a platelet count of 10x10^9/L.[7] The higher target of 50x10^9/L utilized for most patients in our retrospective study would naturally cost considerably more, in terms of financial cost to the patients, infusion room time and transportation costs (outpatients), prolongation of hospital stays (inpatients) and burden on the finite resource of blood products.

Another relevant issue is that of platelet refractoriness, defined as repeated, inadequate response to platelet transfusions. Rates of platelet refractoriness may be as high as 21.6%

among inpatients requiring platelet transfusions, adding both to the complexity of caring for such patients, particularly if and when bleeding does occur, and to those additional costs mentioned above including monetary (increased mean hospitalization cost of $66,000 in the year 2000) and resource utilization (17.8 additional units of platelets/patients).[8]

Furthermore, platelet refractoriness may be a sign of the bigger issue of alloimmunization (defined as platelet refractoriness due to antibodies against antigens found in >25% of platelet donors), a major issue among patients undergoing repeated cycles of chemotherapy or stem cell transplant, requiring long term platelet support. Alloimmunized patients require HLA-matched platelet units from matched/directed donors, adding further to the expense and stress on resources. This is a common problem, affecting approximately five patients on the combined leukemia and transplant services at any given time.

2.3 Transfusion Threshold Rationale

As indicated above, we have demonstrated medical, financial and resource costs with the current institutional approach of transfusing to a threshold of $50x10^9$/L. We hypothesize that a decreased threshold will lead to decreased rates of transfusion-related complications, decreased burden on patients who require frequent transfusions in the inpatient and outpatient setting and decreased financial and resource burden. The rationale behind the experimental threshold of $30x10^9$/L arises from expert consensus, including experts in transfusion medicine and anticoagulation at our own institution and is being used in clinical practice at a number of other centers across North America with various anticoagulation strategies.[9] Furthermore, this lower threshold is the most often used in our own institution for patients who are unable to maintain platelet counts >$50x10^9$/L.

2.4 Risks/Benefits

The primary risk of a decreased platelet transfusion threshold would be that of increased bleeding rates. Platelet-type, or bleeding due to defects of primary hemostasis, tends to be primarily mucocutaneous, including epistaxis, gum bleeding and menorrhagia,[10] rather than into soft tissue, joints or body cavities as with disorders of secondary hemostasis (clotting factor deficiencies, including those induced by anticoagulation). Thrombocytopenic bleeding in the unanticoagulated population is largely low grade (WHO grade 2 or less) and rarely requires intervention beyond platelet transfusion.[6,11]

Potential benefits of a decreased platelet transfusion threshold are numerous. Objective benefits to the individual patient might include decreased rates of transfusion-related complications, including transfusion reactions, infections, volume overload and alloimmunization. Subjective benefits of decreased transfusion frequency/requirement might include improved sense of well-being and quality of life, particularly for outpatients who may require fewer trips for medical care and benefit from increased time at home. Systemic benefits might include decreased overall cost of care and decreased drain on resources, of particular importance when blood products are in short supply.

3.0 OVERVIEW OF CLINICAL TRIAL

3.1 Study Objectives

3.1.1 Primary Objective

1. To determine feasibility of a randomized controlled trial comparing two different platelet transfusion thresholds (50 x10^9/L vs 30 x10^9/L) in patients with treatment or malignancy-induced thrombocytopenia requiring therapeutic anticoagulation.

3.1.2 Secondary Objectives

1. To report outcomes as they would be in a definitive study including:
    a. Progressive or new VTE
    b. Progressive or new ATE
    c. Hemorrhagic events (WHO grade 2 or greater)
    d. A composite of a, b and c.
    e. Major bleeds (WHO grade 3 or 4)
    f. Number of platelet transfusions per patient during the study period
    g. Platelet transfusion related complications (including transfusion reactions, alloimmunization and volume overload)
    h. Degree to which platelet target thresholds are achieved

3.2 Study Population

The study population will include patients undergoing therapy for hematologic malignancy, including HSCT and/or curative-intent chemotherapy in the setting of acute leukemia at the Seattle Cancer Care Alliance/University of Washington Medical Center. All patients must be experiencing treatment-related thrombocytopenia during a time period for which their treating physician has determined anticoagulant therapy for VTE is necessary and appropriate.

3.3 Study Design

This will be a feasibility/pilot study designed to assess the feasibility of a randomized, controlled trial, comparing a lower platelet transfusion threshold (30x10^9/L) to a higher platelet threshold (50x10^9/L) in patients who require anticoagulation for VTE in the setting of treatment-induced (either chemotherapy or HSCT) thrombocytopenia for hematologic disease.

We are targeting an enrollment of approximately 1 patient per month. Patients will be enrolled and randomized in a consecutive fashion to minimize selection bias. Blinding will not be feasible in this study.

3.3.1 Primary Endpoint

The primary endpoint of this study will be feasibility of an RCT comparing a lower platelet transfusion threshold (30x10^9/L) to a higher platelet threshold (50x10^9/L) in patients who require anticoagulation for VTE. To assess feasibility of a multicenter RCT we will evaluate:

1. Number of patients eligible, reasons for ineligibility
2. Number of eligible patients approached for the study

3. Number of patients consenting to enrollment
4. Number of patients successfully following protocol (defined as receiving transfusions 'on protocol' at the end of the study period)

This data will then assist in determining the number of centers likely to be required to appropriately power a definitive study within 2-3 years.

3.3.2 Secondary Endpoints

1. Progressive or new VTE
2. Progressive or new ATE
3. Hemorrhagic events (WHO grade 2 or greater)
4. A composite of a, b and c.
5. Major bleeds (WHO grade 3 or 4)
6. Number of platelet transfusions per patient during the study period
7. Platelet transfusion related complications
   a. transfusion reactions
   b. alloimmunization
   c. volume overload
8. Percent of days on which subjects are transfused (or transfusions are not given) in compliance with the threshold to which they were randomized

3.4 Estimated Accrual

We estimate an accrual rate of approximately one patient per month over a 12-month period. Based upon historical data we estimate approximately 25-30 patients per year will be eligible and are estimating a 45% rate of consent.

3.5 Funding Source

This study will be unfunded, but the PI receives salary source from a T32 grant funded by the National Institute of Health (T32HL007093).

4.0 SAFETY CONSIDERATIONS

4.1 Stopping Rules

The study will be stopped early if major bleeding (WHO grade 3 or greater) is noted in 3 or more patients on the experimental arm once eight patients have been enrolled (and at least four randomized to the experimental arm).

5.0 SUBJECT ELIGIBILITY

5.1 Inclusion Criteria

5.1.1 Any patient with non-APL acute leukemia (AML, ALL, biphenotypic leukemia) undergoing curative intent chemotherapy

OR

Any patient undergoing allogeneic HSCT for a hematologic disorder (including acute leukemia as above, CML, CLL, MDS, primary or secondary myelofibrosis, hypereosiniophilic syndromes, plasma cell disorders, B-cell or T-cell lymphoma)

5.1.2 Disease may be measurable or non-measurable

5.1.3 Age ≥ 18 years of age

5.1.4 Diagnosis of, symptomatic venous thromboembolism requiring therapeutic-dose anticoagulation (unfractionated or low-molecular weight heparin or oral anticoagulants) throughout the period of hematopoietic recovery.

5.1.5 Anticipated platelet count ≤ 50 $x10^9$/L for ≥ 5 days within 72 hours of enrollment

5.1.6 Ability to understand and the willingness to sign a written informed consent document

5.2 Exclusion Criteria

5.2.1 Separate episode of VTE or arterial thrombosis within 3 months of enrollment

5.2.2 Major bleed (WHO Grade 3 or 4) within 6 months of enrollment

5.2.3 Active bleeding (Grade 2 or higher) at the time of enrollment

5.2.4 History of intracranial bleeding at any time

5.2.5 Disorders of hemostasis including von Willebrand Disease, hemophilia, platelet function disorders

5.2.6 Concomitant use of aspirin or non-steroidal anti-inflammatory drugs

5.2.7 Evidence of disseminated intravascular anticoagulation (DIC) as determined by the patient's primary provider.

5.2.8 History of alloimmunization (defined as platelet refractoriness with PRA >25%) at the time of or prior to enrollment

5.2.9 Uncontrolled or concurrent illness including, but not limited to, ongoing or active infection, unstable angina pectoris.

5.2.10 Psychiatric illness/social situations that would limit compliance with study requirements.

5.2.11 Pregnant or able to become pregnant and unwilling to use two forms of birth control during the study period

6.0 Subject Registration

Subjects will be identified either by patient care teams or by study personnel and then approached by study personnel following discussion with the patient's attending physician. To complete the registration process, the PI, Fred Hutch/UW Study Coordinator or designee will assign a patient study number, register the patient on the study, and enter the patient into the Protocol Accrual Tracking System (PATS). A complete, signed, study consent and HIPAA consent are required for registration.

7.0 Treatment Plan

This study is a single-center, open-label randomized pilot study of a platelet transfusion threshold of 30 x10^9/L vs 50x10^9/L among patients receiving anticoagulation for, symptomatic VTE during periods of thrombocytopenia related to the treatment of hematologic malignancies at the Fred Hutchinson Cancer Research Center/University of Washington Seattle Cancer Care Alliance.

7.1 Treatment Plan Overview

In this pilot study, patients meeting the inclusion/exclusion criteria and their primary hematologists are asked whether or not they would agree to participate in the randomized treatment assignment (Appendix 1). Patients agreeable to randomization will be assigned in a 1:1 ratio to a higher (50x10^9/L) or lower (30x10^9/L) platelet transfusion threshold. For those who wish not to be randomized the reason to decline randomization will be recorded, and patients will be managed according to the discretion of their primary hematologist.

7.2 Baseline/Pre-Treatment Assessment

The following procedures will be obtained at baseline before randomization to establish trial eligibility and allow patient characterization. Results of tests and/or procedures conducted as per standard of care will be used to determine study eligibility.

- Medical history including disease and treatment specifics of both the hematologic malignancy and the venous thrombosis, history of bleeding and anti-thrombotic therapy including anticoagulation and antiplatelet agents.
- Targeted physical exam for evidence of bleeding, thrombosis and volume status
- Most recent complete blood counts (assessed within 3 days of study day 0)
- Most recent coagulation assays, including PT, PTT (within one week of study day 0) and fibrinogen (if available).
- CT scan, V/Q scan, Doppler ultrasound or other appropriate diagnostic modality to document VTE diagnosis.

7.3 Randomization

Randomization may be obtained after or up to 72 hours before the platelet count drops below 50x10^9/L, as long as the period of thrombocytopenia (platelet count <50x10^9/L in the absence of platelet transfusion support) is anticipated to last for ≥ 5 days. Following randomization, patients will receive platelet transfusions on all days when the morning platelet count is below the threshold to which they have been randomized. Platelet counts should be checked according to standard of care (daily while inpatient, ≥ 3 times per week while outpatient).

7.4 Administration of Transfusions

The decision to administer a platelet transfusion will be based upon the first platelet count of the day (whether inpatient or outpatient). Transfusions will be administered when the count is below the randomized threshold and will be administered according to institutional policy. Post-transfusion counts will not be routinely checked unless there is reasonable expectation on the part of the subject's primary providers that a single transfusion will be insufficient to achieve a platelet count greater than the specified transfusion threshold. This would include a pre-transfusion platelet count >25x10^9/L below the transfusion threshold or suspicion of alloimmunization or other platelet refractory state. If the post-transfusion check is below the specified threshold, an additional transfusion will be given. In the instance that a morning

platelet count is above the designated threshold and a repeat count, performed later in the day for clinical reasons (eg prior to a procedure), is below the threshold, transfusion is allowed at that time. Counts should not be repeated in a patient not meeting transfusion criteria on morning labs in the absence of another clinical indication.
Transfusions may be either single-donor apheresis units or pooled units, depending on availability and the clinical situation. Type and volume of each transfusion will be documented.

7.5 Concomitant Medication and Supportive Care Guidelines

Pre-medications, including acetaminophen, diphenhydramine and hydrocortisone may be administered in patients with a history of transfusion reaction. In the event of a new, suspected transfusion reaction, supportive care should be administered urgently according to institutional protocol and/or the discretion of the treating provider.

Therapeutic anticoagulation should be given with one of the following agents/dosing strategies.

7.5.1 Unfractionated heparin (UFH)

Heparin should be administered intravenously and may be given with or without a loading bolus(80 units/kg). The initial infusion should be 18 units/kg/hr and should be titrated according to a goal PTT of 60-100 seconds. Re-bolus for low PTT may be given at provider discretion (https://depts.washington.edu/anticoag/home/content/heparin-infusion-guidelines).

7.5.2 Low molecular weight heparin (LMWH)

LMWH may be administered either as enoxaparin or dalteparin. Enoxaparin should be administered at a dose of 1mg/kg subcutaneously every 12 hours for the first 30 days following diagnosis of VTE, after which dosing may be reduced to 1.5mg/kg daily. Dalteparin should be administered at a dose of 200 units/kg for a minimum of 30 days following diagnosis of VTE, after which dosing may be reduced to 150 units/kg daily.

7.5.3 Anticoagulation Dosing Modifications

Dosing modifications may be made to the above regimens for low body weight, obesity, or renal impairment according to the appropriate algorithms found at https://depts.washington.edu/anticoag/home/.

If temporary discontinuation of anticoagulation or reduction to prophylactic dosing is considered to be necessary by the treating provider (such as in the peri-operative or peri-procedure setting), these changes may be made at the provider's discretion for up to a 72 hour period. If anticoagulation must be held or given at a lower dose for longer than 72 hours, randomization will be broken and transfusions will be administered at the discretion of the managing provider(s). The new threshold and anticoagulation regimen will be noted and the patient will be followed for outcomes until the conclusion of a 30-day period from the date of randomization.

7.6 Transfusion Delays/Modifications

The transfusion threshold may be temporarily increased (for up to 72 hours) if a higher platelet count is required for safety in the setting of a procedure (including lumbar puncture and central

line placement). Transfusions according to the randomized threshold should resume once the procedure has been completed and bleeding risk has returned to baseline as determined by the proceduralist and/or the subject's primary provider.

Transfusion thresholds may also be temporarily increased for minor bleeding events which do not meet criteria for grade 3 or 4 bleeding but are bothersome to the patient (e.g. brief but recurrent episodes of epistaxis, vaginal bleeding). If benefit is achieved and the patient or provider feel an increased transfusion threshold is required beyond 72 hours, or if this occurs on three or more occasions during the study period, randomization will be broken and transfusions will be administered at the discretion of the managing provider(s). The new threshold will be noted and the patient will be followed for outcomes until the conclusion of a 30-day period from the date of randomization.

If post-transfusion thresholds are checked and patients are noted to be platelet refractory (defined as a $<5x10^9$/L increase in platelet count 30 minutes following a transfusion on ≥ 2 occasions) efforts should be made, according to institutional protocol and at the discretion of the provider, to optimize transfusion strategy, including the use of HLA-matched units, if necessary. If the subject remains refractory, despite all available interventions, and unable to achieve the targeted platelet threshold, the decision to continue or withhold anticoagulation will be made at the discretion of the primary provider and the patient will break randomization and be taken off protocol.

Possible reasons for transfusion delay include need for specific (eg HLA-matched in the instance alloimmunization develops during the study period) platelets which may not be immediately available or lack of resources (ie infusion room beds or nurses). A delay of no more than 24 hours will be acceptable in either case. Should matched platelets not be available for a period > 24 hours, pooled platelets should be administered. If matched platelets are unavailable for >48 hours and/or frequently unavailable the patient will break randomization and be taken off protocol. Anticoagulation may be continued or discontinued according to the managing provider.

7.7 Duration of Therapy

Patients will remain on protocol until (1) the platelet count spontaneously recovers to $>50\ x10^9$ for three consecutive days, in the absence of transfusions or (2) for a maximum of 30 days after the date of randomization, whichever is shorter. The study period is defined as the period between the first on-study day (post-randomization) with platelet count $<50x10^9$ and either of these endpoints regardless of whether the patient receives transfusions according to protocol or not. Following conclusion of the study period, transfusion thresholds will be determined by each subject's primary provider.

7.7.1 Breaking Randomization

Randomization may be broken and the patient taken off protocol for any of the following reasons. In all cases the new threshold will be noted and the patient will be observed for primary and secondary outcomes until the completion of the study period.

Randomization will be immediately broken and transfusions managed according to the subject's managing provider(s) for any grade 3 or 4 bleeding event. The new threshold will be noted and the patient will be followed for outcomes until the end of the study period. If a grade 3 event completely resolves in <72 hours, is non-life-threatening, does not require permanent discontinuation of anticoagulation and is not reasonably expected to recur (eg vaginal bleeding resolved with hormonal therapy, bleeding from a wound which has been closed), the patient and primary provider may elect to continue with the randomized threshold.

For subjects in whom discontinuation of anticoagulation is deemed necessary by managing providers, randomization will be broken, and a new transfusion threshold will be determined at the discretion of the managing team.

7.8 Duration of Follow-Up

Follow-up after completion of the study period will involve a single, in-person or telephone visit which will occur 30 +/- 5 days after the end of the study period. The visit will include chart review, verbal history and, if appropriate, a brief physical exam for evidence of bleeding or thrombosis.

8.0 Subject Evaluation

8.1 Primary Endpoint

As this is a feasibility study, the primary goal is to determine the number of centers and duration of study that would be required to appropriately power a multicenter trial to evaluate for noninferiority. Toward this aim number of patients eligible, reasons for ineligibility, number of eligible patients approached for the study number of patients consenting to enrollment and number of patients successfully following protocol will be reported and used, according to the table below, to design a larger trial As patients may break randomization and go off protocol for a number of reasons (described in section 9.0 below), the proportion of patients remaining on protocol at the end of the study period will be a second key measure of feasibility.

# Eligible patients/year	% Eligible patients consented	Number of sites	Years of duration
< 15	20-30	50	2
	30-40	35	2
	40-50	28	2
15 - 25	20-30	25	2
	30-40	18	2
	40-50	15	2
>25	20-30	17	2
	30-40	12	2
	40-50	9	2
< 15	20-30	33	3
	30-40	24	3
	40-50	19	3
15 - 25	20-30	17	3
	30-40	12	3

	40-50	10	3
>25	20-30	12	3
	30-40	8	3
	40-50	7	3

8.2 Secondary Endpoints

Secondary endpoints will be monitored and reported as in a full, randomized controlled trial. Endpoints will be defined in the following way.

8.2.1 Progressive or new VTE

All diagnoses of new or progressive VTE will require imaging confirmation, defined as intraluminal filling defect(s) on contrast-enhanced computed tomography (CT) or incompressible venous segment(s) on ultrasonography. In the absence of these studies, a new mismatched segmental defect or a greater perfusion defect compared with baseline on a ventilation/perfusion (V/Q) scan, will also be considered confirmatory. A diagnosis of progression will require unequivocal extension of thrombus on repeat imaging. Presence or absence of symptoms (including pain and swelling in the setting of VTE, pain, dyspnea, hypoxia, tachycardia or hypotension in the setting of PE) will be documented. Events will be independently adjudicated by physicians blinded to the predictor data.

8.2.2 Progressive or new ATE

Diagnoses of new ATE will require either (1) documented acute electrocardiographic (EKG) changes compatible with myocardial injury and/or serum biochemical changes diagnostic of myocardial infarction (2) documented imaging (CT or magnetic resonance imaging (MRI)) changes compatible with infarct due to embolism in the presence of a new neurological deficit (3) imaging demonstrated intraluminal filling defects in an arterial distribution accompanied by symptoms of acute ischemia (acute onset pain, pallor, loss of pulses or other end-organ damage).

8.2.3 Hemorrhagic events (WHO grade 2, 3 or 4)

Hemorrhagic events will be defined according to the WHO bleeding criteria (Appendix 3). Grade 3 events will be defined as events requiring packed red cell transfusions over and above the subject's routine transfusion needs. This will be determined based on the clinical judgment of an investigator.

8.2.4 Number of platelet transfusions

Only transfusions administered during the study period will be included. Transfusions administered 'off protocol' or inappropriately while 'on protocol' will also be counted. Type (apheresis unit or pooled packs) and volume of transfusion will also be noted.

8.2.5 Platelet transfusion related complications

Platelet transfusion reactions will be defined as any of the following (1) new onset fever, chills, hypoxia, urticarial rash or hemodynamic instability during or within 1-2 hours of administration of a transfusion with or without hemolysis (2) transfusion related lung injury (TRALI) defined as new onset dyspnea/tachypnea and hypoxia within 6 hours of transfusion, accompanied by bilateral pulmonary edema on imaging, with or without fever and hypotension.

Volume overload will be defined as evidence of edema (pulmonary, extremity or other dependent area) on exam and/or imaging, requiring treatment with diuretics and/or dialysis. Contribution of platelet transfusions to volume overload will be determined based on the clinical judgment of an investigator.

Alloimmunization will be defined as a combination of platelet refractoriness (as defined in section 7.6) accompanied by a panel reactive antibody result of >25%.

8.2.6 Percent of days on which subjects are transfused (or transfusions are not given) in compliance with the threshold to which they were randomized

Study staff will determine the appropriateness of transfusion management (in accordance with the protocol) each on-protocol day of the study period. The frequency with which transfusions are given despite a platelet count above the determined threshold (not including 72 hour temporary increases or procedures as outlined in section 7.6) will be documented, as will the frequency with which transfusions are not administered within 24 hours after a platelet count below the determined threshold.

8.1 On-Study Clinical Evaluations

Targeted history and physical exam, bleeding diaries and FACT-Th18 questionnaires (Appendix 4) will be conducted in the manner outlined below. Laboratory studies will be conducted per standard of care in this institution, which is a minimum of three times per week.

8.1.1 Inpatient On-Study Visits

While inpatient at the University of Washington Medical Center, patients will be seen three times per seven-day period, visits should be as close to every other day as possible and no more than 3 days apart.

8.1.2 Outpatient On-Study Visits

While outpatients, being followed at the Seattle Cancer Care Alliance, patients will be seen weekly on the same day as other routinely scheduled care (eg clinic visits, nursing assessments, infusion center visits). Visits should be as close to every seven days as possible and no more than 12 days apart.

8.1.3 On-Study Visit Procedures

The following tests and procedures are completed, although not all tests may be done at each visit.

- Targeted history for symptoms of bleeding or thrombosis
- Targeted physical exam for symptoms of bleeding or thrombosis, volume overload
- Most recent complete blood counts (assessed within one day)

- FACT-Th18 Questionnaire (Appendix 5) will be completed weekly
- Bleeding diary (Appendix 4) will be reviewed at each visit and collected weekly
- Additional chart review including but not limited to documentation of suspected hemorrhage, thrombosis and/or transfusion reaction, transfusion administration, vascular imaging data, administration of anticoagulants, antiplatelet agents, antifibrinolytic or other pro-coagulant therapies and/or diuretics, dialysis for volume overload.

8.1.4 End of Treatment (EOT) Visit Schedule and Procedures

This visit will occur on the first outpatient visit following platelet count recovery (within one week) or within three days of count recovery in the inpatient setting. Procedures will include a verbal history of any bleeding or thrombotic symptoms, focused physical exam for evidence of eithers, FACT-Th18 questionnaire and results of the most recent complete blood count ordered by the patient's provider.

9.0 Subject Discontinuation of Active Treatment

Randomization may be broken and active treatment discontinued for any of the reasons outlined in section 7.7.1. Additionally, active treatment may be discontinued for any of the following reasons.

9.1 All reasons for discontinuation of treatment must be documented and the study team must be notified within 24 hours if a subject discontinues treatment. Reasons include:

9.1.1 Completion of protocol treatment.

9.1.2 Initiation of any malignancy-directed therapy other than that being given at the time of randomization

9.1.3 Withdrawal of consent; the patient may withdraw from the study at any time for any reason.

9.1.4 At investigator's discretion

9.1.5 Pregnancy

9.1.6 Grade 3 or 4 bleed (Appendix 3)

9.1.7 progressive or new VTE or ATE requiring change in antithrombotic management

9.2 For any reason other than withdrawal of consent, subjects will continue to be observed for the study period (until platelet count recovery or 30 days from randomization, whichever comes first). They will also have the same 30 day follow up (described in section 7.8) as patients who remain on active treatment.

10.0 Adverse Events

10.1 Expedited Reporting Requirements

In accordance with Fred Hutch/UW Cancer Consortium IRB policy, all adverse events (AEs; whether occurring on-site or off-site), which in the opinion of the principal investigator (PI) are (1) unexpected, and (2) related or possibly related to the research, and (3) serious or suggests

that the research places research participants or others at a greater risk of physical or psychological harm than was previously known or recognized, will be submitted to the IRB within ten (10) calendar days of learning of the problem. Both the "Expedited Reporting Form for Unanticipated Problems or Noncompliance" and the "Adverse Event Reporting Form", or equivalent forms, will be completed for this reporting.

10.2 Definitions

10.2.1 Adverse Event (AE): Any harm or untoward medical occurrence in a research participant administered a medical product, medical treatment or procedure even if it does not necessarily have a causal relationship with the product, treatment, or procedure. An adverse event can be any unfavorable and unintended sign (including an abnormal laboratory finding, for example), symptom, or disease temporally associated with the use of a medical product, medical treatment, or procedure whether or not considered to be related. Mechanisms of obtaining information on AE include study visits, hospital progress and discharge notes.

10.2.2 Related or Possibly Related AE: An AE is "related or possibly related to the research procedures" if in the opinion of the principal investigator, it was more likely than not caused by the research procedures. AEs that are solely caused by an underlying disease, disorder or condition of the subject or by other circumstances unrelated to either the research or any underlying disease, disorder or condition of the subject are not "related or possibly related". If there is any question whether or not an AE is related or possibly related, the AE should be reported.

10.2.3 Serious AE (SAE): An adverse event that results in any of the following outcomes:

- Death
- Life-threatening adverse event (real risk of dying)
- Prolongation of hospitalization*
- Persistent or significant disability/incapacity/or change in psychosocial status
- Congenital anomaly
- Requirement of intervention to prevent permanent impairment or damage

*Hospitalization itself will not be considered a serious adverse event if required for complications or treatment of the underlying hematologic malignancy, treatment or comorbid conditions. Hospitalization will be considered a SAE if it fulfills the criteria for a serious and unexpected adverse event as otherwise described.

10.2.4 Unexpected AE: An unexpected adverse event is defined as an event that has a nature or severity, or frequency that is not consistent with the applicable investigator brochure, or the prior medical condition of the subject or other treatment given to the subject. "Unexpected," as defined in this study, refers to an adverse experience that has not been previously observed and reported in patients requiring anticoagulation and/or experiencing thrombocytopenia.

10.3 Grading Adverse Event Severity

All bleeding will be graded in severity according to the WHO criteria (Appendix 3). All other (unexpected) AEs will be graded in severity according to the NCI Common Terminology Criteria for Adverse Events (CTCAE) Version 4.0 (http://ctep.cancer.gov). If a CTCAE criterion does not exist, the investigator should use the grade or adjectives: Grade 1 (mild), Grade 2 (moderate),

Grade 3 (severe), Grade 4 (life-threatening), or Grade 5 (fatal) to describe the maximum intensity of the adverse event.

10.4 Monitoring, Recordings, and Standard Reporting of Adverse Events

Only grade ≥2 adverse events will be recorded, graded, and reported as appropriate per 10.1. Grade ≤ 3 heme AEs are anticipated for all subjects based upon inclusion criteria, are not anticipated to be related to study procedures and will not be reported. Grade 4 heme AEs will be reported, however. AEs will be collected for the duration that the patient remains on protocol. If a subject decides to terminate the study early or breaks randomization or any of the reasons described in 7.7.1 their medical record will continue to be followed for AEs for the study period as defined in 7.6. AEs that do not meet the requirement for expedited reporting will be reported to the IRB as part of the annual renewal of the protocol.

10.5 Adverse Event Recording Period

AEs will be monitored and recorded in the study database from the first time the subject is simultaneously (1) randomized to a transfusion threshold and (2) experiences a platelet count $<50x10^9$/L to the end of the study period. AEs with an onset date prior to the first day of the study period will not be recorded, except in the case of clinically significant worsening of the AE during the specified AE monitoring time frame.

11.0 Data and Safety Monitoring Plan

Institutional support of trial monitoring will be in accordance with the Fred Hutch/University of Washington Cancer Consortium Institutional Data and Safety Monitoring Plan. Under the provisions of this plan, Fred Hutch Clinical Research Support (CRS) coordinates data and compliance monitoring conducted by consultants, contract research organizations, or Fred Hutch employees unaffiliated with the conduct of the study. Independent monitoring visits occur at specified intervals determined by the assessed risk level of the study and the findings of previous visits per the institutional DSMP.

In addition, protocols are reviewed at least annually and as needed by the Consortium Data and Safety Monitoring Committee (DSMC), Fred Hutch Scientific Review Committee (SRC) and the Fred Hutch /University of Washington Cancer Consortium Institutional Review Board (IRB). The review committees evaluate accrual, adverse events, stopping rules, and adherence to the applicable data and safety monitoring plan for studies actively enrolling or treating subjects. The IRB reviews the study progress and safety information to assess continued acceptability of the risk-benefit ratio for human subjects. Approval of committees as applicable is necessary to continue the study.

The trial will comply with the standard guidelines set forth by these regulatory committees and other institutional, state and federal guidelines.

12.0 Data Management/Confidentiality

Research data will be recorded in a study-specific, password protected database using a unique study ID for each patient to assure patient confidentiality. Data from source documents will be transcribed into this database. Source documents are documents where patient data are recorded and documented for the first time. They include, but are not limited to, hospital

records, clinical and office charts, laboratory notes, memoranda, quality of life assessments, pharmacy dispensing records, recorded data from automated instruments, copies of transcriptions that are certified after verification as being accurate and complete, X-rays, patient files, and records kept at the pharmacy, laboratories, and medico-technical departments involved in the clinical trial. There will be no case reports forms (CRFs) used for this trial.

The investigator will ensure that data collected conform to all established guidelines. Each subject is assigned a unique subject number to protect subject confidentiality. Subjects will not be referred to by this number, by name, or by any other individual identifier in any publication or external presentation. The licensed medical records department, affiliated with the institution where the subject receives medical care, maintains all original inpatient and outpatient chart documents. Patient research files will be maintained under control of the Principal Investigator and/or study team and kept in a locked office or file room within a secure building. Access to the study database will be restricted by electronic password protection and restricted access to computers (i.e., locked offices).

13.0 Statistical Considerations

13.1 Study Design

This is a pilot study of two different platelet transfusion thresholds in patients receiving anticoagulation during periods of thrombocytopenia related to the treatment of hematologic malignancies. Patients will be randomized to transfusion thresholds in a 1:1 fashion.

13.2 Primary/Secondary Endpoints/Hypotheses and Analytical Methods

The primary endpoints of this study are (1) enrollment and (2) compliance. Enrollment will be described at the end of a 12-month period and (2) compliance will be evaluated as described in section 3.3.1. The secondary endpoints described in sections 3.3.2 will also be reported and analyzed with descriptive statistics only. This trial is not powered to detect statistically significant differences between the study arms for these clinically important endpoints. Rather, the primary goal is to establish feasibility for enrollment into a formal trial.

13.2 Sample Size and Power

As this study is purely descriptive, it will not be powered to determine efficacy or safety of either intervention. The sample size has been chosen based upon the rate of enrollment necessary to establish the feasibility of an appropriately powered study.

A full trial would be a non-inferiority study powered for safety. The primary outcome would be WHO Grade 2 or above bleeding and the study would be powered to identify a relative risk of 1.4 or greater. This is based upon trials of anticoagulation, in which RR of 1.4 for bleeding is standardly considered to be acceptable.

Based on historical data, we assume a bleeding rate of ≥40% at the higher threshold. A relative risk of 1.4 would correspond to an assumed-true bleeding rate at the lower threshold of 56% (.56/.40 = 1.4). If we assume that the true bleeding rate at the lower threshold is also 40%, then with 125 patients per treatment arm, we'll have approximately 84% power to deem the lower threshold non-inferior to the higher threshold (at the one-sided significance level of .05).

In other words, if the assumed-true bleeding rates in each arm are 40%, then the upper limit to the 95% confidence limit for the difference between the estimate bleed rates (bleed rate at lower threshold – bleed rate at higher threshold) is below 0.16 with a probability of 0.84. If we assume a true bleeding rate of 60% at the higher threshold, then a relative risk of 1.4 (or less) corresponds to an assumed-true rate in the lower threshold of 84% (or less). If the assumed-true bleeding rates in both arms is 60%, then 125 patients/arm yield approximately 99% power to deem the lower threshold as non-inferior (as defined above).
Anticipating a two-year enrollment period across fifteen sites, expecting that other sites will enroll at a slightly lower rate than the primary site randomization of 12 patients in a one-year period at our Center will be a rough benchmark for feasibility (although other factors will be considered when judging this approach as feasible for purposes of designing the randomized Phase III trial, including compliance with the study protocol and event rate).

13.3 Ethnic and Gender Distribution Chart

TARGETED / PLANNED ENROLLMENT: Number of Subjects			
Ethnic Category	**Sex / Gender**		
	Females	**Males**	**Total**
Hispanic or Latino	0	0	0
Not Hispanic or Latino	5	7	12
Ethnic Category Total of All Subjects	5	7	12
Racial Categories			
American Indian / Alaska Native	0	0	0
Asian	0	0	0
Native Hawaiian or Other Pacific Islander	0	0	0
Black or African American	0	0	0
White	5	7	12
Racial Categories: Total of All Subjects	5	7	12

14.0 Investigator Obligations

The PI is responsible for the conduct of the clinical trial at the site and is responsible for personally overseeing the treatment of all study subjects. The PI must assure that all study site personnel, including sub-Investigators and other study staff members, adhere to the study protocol and to all applicable regulations and guidelines regarding clinical trials both during and after study completion.

All subjects are informed of the nature of the program, its possible hazards, and their right to withdraw at any time, and each subject signs a form indicating their consent to participate prior to receiving any study-related procedures.

15.0 Administrative and Regulatory Considerations

15.1 Protocol Interpretation and Compliance

The procedures defined in the protocol are carefully reviewed by the PI and his/her staff prior to the time of study initiation to ensure accurate representation and implementation. Protocol

amendments, if any, are reviewed and implemented promptly following IRB/EC and relevant Competent Authorities approval.

15.2 Ethical Considerations

The Investigator agrees to conduct this study in accordance with applicable United States FDA clinical trial regulations and guidelines, the ICH (E6) GCP guidelines, the IRB/EC and local legal requirements and with the Declaration of Helsinki (1989). The Investigator will conduct all aspects of this study in accordance with all national, state, and local laws of the applicable regulatory agencies.

15.3 Informed Consent

The PI and qualified designees assume the responsibility of obtaining written Informed Consent for each subject or the subject's legally authorized representative before any study-specific procedures are performed.

Subjects meeting the criteria set forth in the protocol will be offered the opportunity to participate in the study. To avoid introduction of bias, the Investigator must exercise no selectivity with regard to offering eligible subjects the opportunity to participate in the study. All candidate subjects will receive a comprehensive explanation of the proposed treatment, including the nature of the therapy, alternative therapies available and other factors that are part of obtaining a proper Informed Consent. Subjects will be given the opportunity to ask questions concerning the study, and adequate time to consider their decision to or not to participate. Informed Consent will be documented by the use of a written Consent Form that includes all the elements required by ICH guidelines. The form is to be signed and dated by the subject or subject's legally authorized representative and by the person who administers the consent process. A copy of the signed form will be given to the person who signed it and the original signed Consent Form will be maintained with the subject's study records. If an amendment to the protocol changes the subject participation schedule in scope or activity, or increases the potential risk to the subject, the Informed Consent Form must be amended. Any amended Informed Consent must be reviewed by the Sponsor or designee and approved by the IRB/EC prior to use. The revised Informed Consent Form must be used to obtain re-consent from any subjects currently enrolled in the study if the subject is affected by the amendment, and must be used to document consent from any new subjects enrolled after the approval date of the amendment.

15.4 Institutional Review Board/Ethics Committee

The PI will assure that an appropriately constituted IRB/EC that complies with the requirements of 21 CFR Section 56 or written assurance of compliance with ICH (E6) guidelines will be responsible for the initial and continuing review and approval of the clinical study. Before initiation of the study, the PI or designee will forward copies of the protocol and Consent Form to be used for the study to the IRB/EC for its review and approval. The PI or designee will also assure that all changes in the research activity and all unanticipated problems involving risks to human subjects or others will be reported promptly to the IRB/EC, and that no changes will be made to the protocol without prior IRB/EC approval, except where necessary to eliminate apparent immediate hazards to human subjects. The Investigator or designee will be responsible for submitting periodic progress reports to the IRB/EC at intervals appropriate to

the degree of subject risk involved in the study, but not less than once per year and at the completion or termination of the study.

16.0 Stopping the Study

The investigators may decide to stop the study at any point, for any reason. The following reasons will lead to premature termination of the trial

- WHO grade 3/4 bleeding rate <30% in the lower transfusion threshold arm following enrollment of 8 patients

References

1. Gerber DE, Segal JB, Levy MY, Kane J, Jones RJ, Streiff MB. The incidence of and risk factors for venous thromboembolism (VTE) and bleeding among 1514 patients undergoing hematopoietic stem cell transplantation: implications for VTE prevention. *Blood*. 2008;112(3):504-510.
2. Carrier M, Khorana AA, Zwicker J, et al. Management of challenging cases of patients with cancer-associated thrombosis including recurrent thrombosis and bleeding: guidance from the SSC of the ISTH. *J Thromb Haemost*. 2013;11(9):1760-1765.
3. Campbell PM, Ippoliti C, Parmar S. Safety of anticoagulation in thrombocytopenic patients with hematologic malignancies: A case series. *J Oncol Pharm Pract*. 2016.
4. Pemmaraju N, Kroll MH, Afshar-Kharghan V, Oo TH. Bleeding Risk in Thrombocytopenic Cancer Patients with Venous Thromboembolism (VTE) Receiving Anticoagulation. *Blood*. 2012;120(21):3408-3408.
5. Samuelson BT, Gernsheimer T, Estey E, Garcia DA. Variability in management of hematologic malignancy patients with venous thromboembolism and chemotherapy-induced thrombocytopenia. *Thromb Res*. 2016;141:104-105.
6. Slichter SJ, Kaufman RM, Assmann SF, et al. Dose of prophylactic platelet transfusions and prevention of hemorrhage. *N Engl J Med*. 2010;362(7):600-613.
7. Campbell HE, Estcourt LJ, Stokes EA, et al. Prophylactic platelet transfusions in patients with blood malignancies: cost analysis of a randomized trial. *Transfusion*. 2014;54(10):2394-2403.
8. Meehan KR, Matias CO, Rathore SS, et al. Platelet transfusions: utilization and associated costs in a tertiary care hospital. *Am J Hematol*. 2000;64(4):251-256.
9. Miao Y, Soff GA, Parameswaran R, Wills J, Mantha S. Enoxaparin Dose Reduction for Thrombocytopenia in Patients with Cancer: A Quality Assessment Study. *Blood*. 2015;126(23):429-429.
10. Kirchmaier CM, Pillitteri D. Diagnosis and Management of Inherited Platelet Disorders. *Transfus Med Hemother*. 2010;37(5):237-246.
11. Stanworth SJ, Estcourt LJ, Powter G, et al. A no-prophylaxis platelet-transfusion strategy for hematologic cancers. *N Engl J Med*. 2013;368(19):1771-1780.

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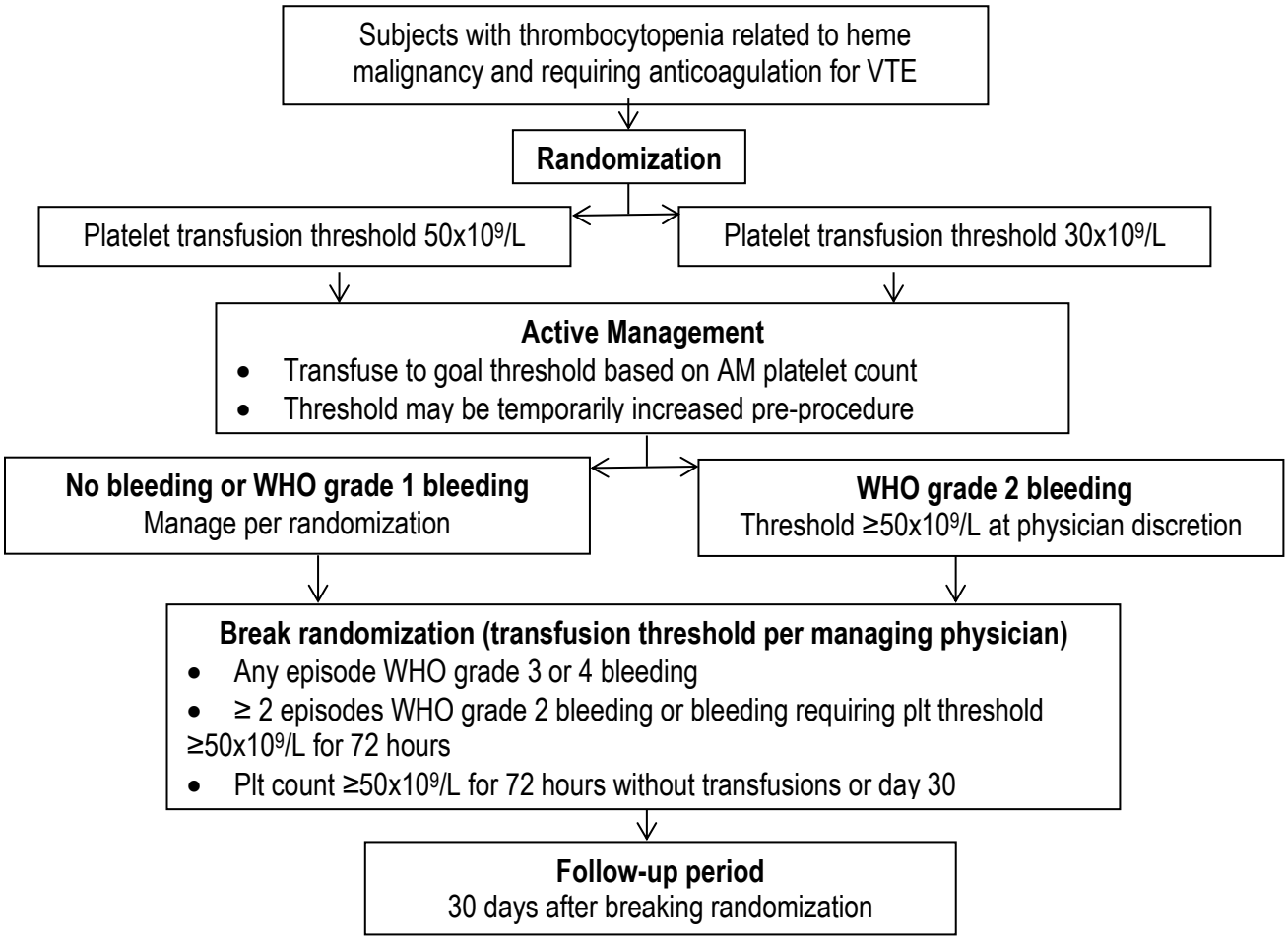
Document Release Date: 12/27/2017

Appendix 1: Trial Screening, Entry, Randomization, Treatment and Monitoring Flow Diagram



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Appendix 2: Data Collection Throughout the Study

Study Period	**Data Collection**
Screening	Age, gender Diagnosis and treatment 6 month bleeding/thrombosis history (including active bleeding) *If ineligible:* reason for ineligibility
Consent	*If consent refused:* reason for refusal
Enrollment	Malignancy diagnosis and treatment Lifetime bleeding/thrombosis history Transfusion history Anticoagulation plan (per managing physician) Weight, CBC, metabolic panel
Active management	Daily platelet count Platelet transfusion threshold (and reason for deviation if present) Transfusion data (product, number, response when available) Daily bleeding assessment VTE symptom assessment Anticoagulation management (missed or held doses)
30 Day Follow-up	Platelet count Current platelet threshold Current anticoagulation plan 30 day bleeding/thrombosis history

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Appendix 3: World Health Organization Bleeding Scale

	Grade 1	Grade 2	Grade 3
Oral and nasal	➢ Oropharyngeal bleeding – total duration of all episodes in previous 24 hours ≤ 30 minutes* ➢ Petechiae of oral mucosa ➢ Epistaxis – total duration of all episodes in previous 24 hours ≤ 30 minutes*	➢ Oropharyngeal bleeding – total duration of all episodes in previous 24 hours > 30 minutes* ➢ Epistaxis – total duration of all episodes in previous 24 hours > 30 minutes*	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†
Skin, soft tissue, musculoskeletal	➢ Petechiae of skin ➢ Purpura ≤ 1 inch diameter ➢ One or more spontaneous hematomas in the soft tissue or muscle > 1 inch	➢ Purpura > 1 inch diameter ➢ Spontaneous hematoma in deeper tissues ➢ Joint bleeding (confirmed by aspiration, imaging study or other accepted technique)	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†
Gastrointestinal	➢ Positive stool occult blood test‡	➢ Melanotic stool ➢ Hematochezia – visible red blood mixed in stool, not requiring a transfusion ➢ Hematemesis – grossly visible blood in emesis or in nasogastric drainage tube (not related or secondary to swallowed blood)	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†
Genitourinary	➢ Any biochemical or microscopic Hb/RBCs without red urine‡ ➢ Abnormal vaginal bleeding (Unexpected bleeding out of normal cycle *or* bleeding heavier than normal *or* breakthrough bleeding (patient on hormonal therapy to prevent bleeding)) with spotting	➢ Gross/visible hematuria without need for transfusion ➢ Abnormal vaginal bleeding (Unexpected bleeding out of normal cycle *or* bleeding heavier than normal *or* breakthrough bleeding (patient on hormonal therapy to prevent bleeding)) more than spotting	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†

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Pulmonary		➢ Hemoptysis – visible blood ➢ Blood in broncho-pulmonary lavage, or blood tinged sputum (excluding those with nose or oropharyngeal bleeding)	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†
Body cavity		➢ Visible blood in body cavity fluid (e.g. red cells apparent in fluid aspirate) short of criteria for Grade 3 or 4	➢ Grossly bloody body cavity fluids and organ dysfunction with symptoms, and/or need to intervene (e.g. to aspirate), and/or need for transfusion
Central nervous system		➢ Retinal bleeding without visual impairment ➢ Lumbar puncture with blood (>5 RBC/μL in CSF on microscopic analysis and non-traumatic tap), no symptoms and no visible red color	➢ Lumbar puncture with visible red color in absence of symptoms, and non-traumatic tap
Invasive sites		➢ Bleeding at invasive sites (venipuncture sites, intravenous lines or catheter exit sites): active oozing at site for a cumulative total of > 1 hour in the previous 24 hours	➢ Any bleeding requiring RBC transfusion over routine transfusion needs†
Hemodynamic instability			➢ Any bleeding associated with moderate hemodynamic instability (hypotension; >30mmHg fall or >30% decrease in either systolic or diastolic blood pressure) and requiring RBC transfusion over routine transfusion needs†

Grade 4:

- ➢ Any bleeding associated with severe hemodynamic instability (hypotension; >50mm/Hg fall or >50% decrease in either systolic or diastolic blood pressure, with associated tachycardia (heart rate increase of ≥ 20% for 20 minutes) and requiring RBC transfusion over routine transfusion needs
- ➢ Fatal bleeding from any source
- ➢ Retinal bleeding with visual impairment (Visual impairment is defined as a field deficit, and patients with suspected visual impairment require an ophthalmologic consult for documentation)
- ➢ CNS symptoms with non-traumatic bloody lumbar puncture
- ➢ CNS bleeding on imaging study with or without dysfunction

RBC indicates red blood cell; Hb, hemoglobin; CSF, cerebrospinal fluid; Hg, mercury; and CNS, central nervous system

* Count actual bleeding (i.e. "running out" or need for basin, Kleenex, towel, etc.) not minor bleeding

†Red cell transfusion must be specifically related to treatment of bleeding within 24 hours of onset of bleeding

‡Not assessed in PLADO

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Appendix 4: Outpatient Bleeding Diary

Instructions for completing your Bleeding Assessment:

- Please complete this checklist in the morning on a daily basis.
- Please think about what has happened and changed over the past 24 hours.
- If you are concerned about any of your signs or symptoms, contact your doctor: _____
- If you have questions about completing this form, contact your study team: _____
- Call 911 for life threatening emergencies.

Who is filling out this form?		□ Patient □ Caregiver	□ Patient □ Caregiver	□ Patient □ Caregiver	□ Patient □ Caregiver	□ Patient □ Caregiver	□ Patient □ Caregiver	□ Patient □ Caregiver
Location	Did you notice any...	Each morning, answer questions for yesterday: Yes – No – Unsure For example, on Monday, tell us about Sunday						
		___/___ Monday	___/___ Tuesday	___/___ Wednesday	___/___ Thursday	___/___ Friday	___/___ Saturday	___/___ Sunday
Mouth	Bleeding from your gums, inside cheeks, roof of mouth, under tongue or lips?	Yes – more than 30 minutes Yes – less than 30 minutes No Unsure	Yes – more than 30 minutes Yes – less than 30 minutes No Unsure	Yes – more than 30 minutes Yes – less than 30 minutes No Unsure	Yes – more than 30 minutes Yes – less than 30 minutes No Unsure	Yes – more than 30 minutes Yes – less than 30 minutes No Unsure	Yes – more than 30 minutes Yes – less than 30 minutes No Unsure	Yes – more than 30 minutes Yes – less than 30 minutes No Unsure
	Blood blisters in or around your mouth?	Yes – more than 5 Yes – less than 5 No Unsure	Yes – more than 5 Yes – less than 5 No Unsure	Yes – more than 5 Yes – less than 5 No Unsure	Yes – more than 5 Yes – less than 5 No Unsure	Yes – more than 5 Yes – less than 5 No Unsure	Yes – more than 5 Yes – less than 5 No Unsure	Yes – more than 5 Yes – less than 5 No Unsure
Nose	Bleeding from the nose?	Yes – more than 30	Yes – more than 30	Yes – more than 30	Yes – more than 30	Yes – more than 30	Yes – more than 30	Yes – more than 30

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		minutes Yes – less than 30 minutes No Unsure	minutes Yes – less than 30 minutes No Unsure	minutes Yes – less than 30 minutes No Unsure	minutes Yes – less than 30 minutes No Unsure	minutes Yes – less than 30 minutes No Unsure	minutes Yes – less than 30 minutes No Unsure	minutes Yes – less than 30 minutes No Unsure
Skin	Very small red or purple spots on your skin (petechiae, less than 1/8 inch (about the size of a pencil tip)	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure
	If you have these spots, is it new?	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No
	Bruising greater than 1 inch? 1 inch = [redacted]	Yes – 1-2 bruises Yes – many bruises No Unsure	Yes – 1-2 bruises Yes – many bruises No Unsure	Yes – 1-2 bruises Yes – many bruises No Unsure	Yes – 1-2 bruises Yes – many bruises No Unsure	Yes – 1-2 bruises Yes – many bruises No Unsure	Yes – 1-2 bruises Yes – many bruises No Unsure	Yes – 1-2 bruises Yes – many bruises No Unsure
	Is the bruise new?	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No
	If your bruise is not new, is it larger than yesterday?	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No	Yes No
	If you have bruises, how big is the biggest one?	Less than an inch More than an inch	Less than an inch More than an inch	Less than an inch More than an inch	Less than an inch More than an inch	Less than an inch More than an inch	Less than an inch More than an inch	Less than an inch More than an inch

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		More than 4 inches	More than 4 inches	More than 4 inches	More than 4 inches	More than 4 inches	More than 4 inches	More than 4 inches
	4 inches = [redacted]							
Joints/ Muscles	Swelling or pain in your joints or muscles?	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure
	If yes, where?							
Invasive site	Bleeding or oozing near IV site, implanted port, where you had blood drawn, or IV catheters?	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure
	If yes, where?							
	If yes, for how long in minutes?							
Vomit	Bright red, visible bloody streaks, clots, coffee ground like?	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure
Stool	Bright red, bloody streaks, clots, black or	Yes – only on the tissue	Yes – only on the tissue	Yes – only on the tissue	Yes – only on the tissue	Yes – only on the tissue	Yes – only on the tissue	Yes – only on the tissue

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	tarry (sticky black)?	Yes – in the toilet, too No Unsure	Yes – in the toilet, too No Unsure	Yes – in the toilet, too No Unsure	Yes – in the toilet, too No Unsure	Yes – in the toilet, too No Unsure	Yes – in the toilet, too No Unsure	Yes – in the toilet, too No Unsure
Urine	Pink, red, bloody drops, clots?	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure
Vaginal □ Skip if male	Vaginal bleeding, including your period?	Yes – spotting only Yes – flow requiring pads No Unsure	Yes – spotting only Yes – flow requiring pads No Unsure	Yes – spotting only Yes – flow requiring pads No Unsure	Yes – spotting only Yes – flow requiring pads No Unsure	Yes – spotting only Yes – flow requiring pads No Unsure	Yes – spotting only Yes – flow requiring pads No Unsure	Yes – spotting only Yes – flow requiring pads No Unsure
Cough	Are you coughing up blood?	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure
Other Bleeding Symptoms								
If yes, describe:								
Blood Transfusions								
Blood Transfusions	Red blood cells and/or platelet transfusions at a non-study site	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure	Yes No Unsure

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	If yes, where:							

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Appendix 5: Modified FACT-Th18 Questionnaire

Please circle or mark one number per line to indicate your response as it applies to the past 7 days.

		Not at all	A little bit	Some -what	Quite a bit	Very much
An5	I have energy	0	1	2	3	4
An7	I am able to do my usual activities	0	1	2	3	4
Th1	I bleed easily	0	1	2	3	4
Th2	I bruise easily	0	1	2	3	4
Th3	I worry about problems with bruising or bleeding	0	1	2	3	4
Th4	I worry about the possibility of serious bleeding	0	1	2	3	4
Th5	I am bothered by nosebleeds	0	1	2	3	4
Th6	I am bothered by bleeding in my gums or mouth	0	1	2	3	4
Th7	I am bothered by pinpoint bruising beneath my skin	0	1	2	3	4
Th8	I am bothered by blood in my urine or stool	0	1	2	3	4
Th9	I am inconvenienced by platelet transfusions	0	1	2	3	4
HI7	I feel fatigued	0	1	2	3	4
Th 10	I avoid or limit physical activity (because of concern with bleeding or bruising)	0	1	2	3	4
Th 11	I avoid or limit social activity (because of concern with bleeding or bruising)	0	1	2	3	4
Th	I am frustrated by not being able to do my usual activities	0	1	2	3	4
Th 13	I worry that my treatment will be delayed (because of low blood counts)	0	1	2	3	4
Th 14	I worry that my treatment dose will be reduced (because of low blood counts)	0	1	2	3	4
Th	For women only: I am bothered by vaginal bleeding	0	1	2	3	4

Appendix 6: Suggested Management of Grade 3/4 Hemorrhagic Events

Supportive care should be initiated for all grade 3/4 hemorrhagic events. This may include but not be limited to:

- Local control measures, including surgical interventions if indicated
- Platelet transfusion
- PRBC transfusion
- Cryoprecipitate in the event of low fibrinogen
- IV fluids prior to arrival of the above products for hemodynamic instability
- Anti-fibrinolytic agents (e.g. epsilon amino caproic acid or tranexamic acid)

The decision of whether or not to use more aggressive pro-hemostatic interventions (including anticoagulant-specific antidotes, where available) is based on a number of factors, including anticoagulant agent and half-life, time since last dose, renal function and location/severity of bleed. If reversal is deemed necessary by the managing provider, suggested approaches may be found at https://depts.washington.edu/anticoag/home/sites/default/files/GUIDELINES%20FOR%20REVERSAL%20OF%20ANTICOAGULANTS%20February%202016.pdf.