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Rationale and Design of Platelet Transfusions in Hematopoietic Stem cell Transplantation: The PATH Pilot Study

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Abstract

Introduction

In patients with transient thrombocytopenia being treated with high-dose chemotherapy followed by stem cell rescue – Hematopoietic Stem cell Transplantation (HSCT), prophylactic transfusions are standard therapy to prevent bleeding. However, a recent multicenter trial suggests that prophylactic platelet transfusions in HSCT may not be necessary. Additionally, the potential overuse of platelet products places a burden on a scarce health care resource. Moreover, the benefit of prophylactic platelet transfusions to prevent clinically relevant hemorrhage is debatable. Current randomized data compares different thresholds for administering prophylactic platelets or prophylactic vs. therapeutic platelet transfusions. An alternative strategy involves prescribing prophylactic anti-fibrinolytic agents such as tranexamic acid to prevent bleeding.

Methods and Analysis

This report describes the design of an open labelled randomized pilot study evaluating the prophylactic use of oral tranexamic acid with platelet transfusions in the setting of autologous HSCT. In 3-5 centres, 100 patients undergoing an Autologous HSCT will be randomly assigned to either a prophylactic tranexamic acid or prophylactic platelets bleeding prevention strategy based daily hemoglobin values up to 30 days post-transplant. The study will stratified by centre and type of transplant. The primary goal is to demonstrate study feasibility while collecting clinical outcomes on 1) WHO and BSMS Bleeding Scales, 2) Transplant Related Mortality, 3) Quality of Life, 4) Length of Hospital Stay, 5) ICU Admission rates, 6) Bearman Toxicity scores, 7) Incidence of Infections, 8) Transfusion requirements, 9) Adverse reactions and 10) Economic Analyses

Ethics and Dissemination

This study is funded by a peer-reviewed grant from the Canadian Institutes of Health Research (201503) and is registered on Clinicaltrials.gov NCT02650791. It has been approved by the Ottawa Health Science Network Research Ethics Board. Study results will presented at national and international conferences. Importantly, the results of this trial will inform the feasibility and conduct of a larger study.

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INTRODUCTION

1.1 Background and rationale

1.1.1 What is the problem to be addressed?

In Canada, over 1,500 autologous hematopoietic stem cell transplantations (ASCT) are performed annually for hematologic malignancies.[1] It is currently standard practice to provide a prophylactic transfusion of platelets to prevent bleeding when the daily measured platelet count is less than 10 x 10^9/L.[2-5] A patient may require up to six adult platelet doses during the post-transplant period.[6] However, the true benefit of prophylactic platelet transfusions in the ASCT setting is unclear and has been called into question by several recent studies.[7-9] Prophylactic platelet transfusions may not only be unnecessary, they may be detrimental to the patient. Among blood products, platelet transfusions are associated with the highest risk of both infectious and non-infectious complications: this would include bacterial infections and allergic /febrile reactions (Table 1).[10-13] Moreover, the potential overuse of platelet products places a significant burden on a scarce health care resource that is provided through volunteer donations. This concern is further highlighted by the 2 recent "alert" warnings of significant platelet shortages or potential shortages either regionally or nationally issued by the Canadian Blood Services [personal communication, R. Trifulnov, Canadian Blood Services 2015].

An alternative strategy to prevent bleeding and reduce the need for platelet transfusions involves administering Tranexamic Acid, an oral antifibrinolytic agent to stabilize blood clots and reduce bleeding.[14] Tranexamic Acid is safe and effective in many clinical scenarios,[15 16] and may be a reasonable alternative for prophylactic platelet transfusions. In the setting of ASCT, Tranexamic Acid may reduce bleeding and further enhance a strategy of therapeutic platelet transfusions where platelets are administered only in the event of active bleeding symptoms.

The effect of prophylactic platelet transfusions and Tranexamic Acid on clinical, quality of life and economic outcomes in patients receiving ASCT is unknown. Our primary aim is to perform a randomized controlled trial to determine whether a strategy of prophylactic Tranexamic Acid (with therapeutic platelet transfusions) is safe and effective compared to prophylactic platelet transfusions in patients undergoing ASCT. Before conducting a larger trial, we first propose a pilot randomized controlled trial to determine the feasibility of such a study.

1.1.2 Why is a trial needed now?

The evidence supporting the use of prophylactic platelets to prevent bleeding in ASCT is weak and platelets remain the scarcest blood resource with the highest complication rate of all blood products. Patients undergoing transplant represent an important proportion of patients receiving platelet transfusions and there is a need to identify an alternative strategy to prevent and control bleeding in this high risk population. Clinical trials evaluating the effectiveness of platelet transfusions in malignant hematology patients are heterogeneous and have included patients being treated with a variety of modalities, including high-dose chemotherapy, autologous and allogeneic transplantation. They have examined different prophylactic platelet transfusion thresholds, different platelet doses, and a solely therapeutic platelet transfusion strategy (i.e. no

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Tranexamic Acid or other antifibrinolytic agent). In the latter circumstance, a therapeutic platelet transfusion strategy did not appear to increase bleeding in subgroup analyses of patients undergoing ASCT.[7 9] A strategy of prophylactic Tranexamic Acid combined with therapeutic platelet transfusions may reduce bleeding, platelet transfusions and the adverse consequences associated with platelet transfusions.

1.1.3 Platelet Transfusion Requirements in Autologous Stem Cell Transplantation

In Canada, over 1,500 ASCT are performed annually.[1] A patient undergoing ASCT typically receives 2-6 adult platelet doses in the post-transplant period.[6 7 9] All adult transplant centres in Canada routinely prescribe prophylactic platelet transfusions when the daily measured platelet count is less than 10 x 10^9/L.[17] Indeed, this is the practice at our centre, where an average of 6 adult platelet doses are transfused in the first 30 days following transplant.[6]

1.1.4 Are Prophylactic Platelet Transfusions Beneficial?

The practice of prophylactic platelet transfusions began following the publication of an observational study in acute leukemia patients in the early 1960s that observed an increase in the number of days with bleeding with worsening thrombocytopenia.[18] However, the onset of major bleeding was not clearly related to a specific platelet threshold. Moreover, a review of 3000 thrombocytopenic adult oncology patients over a 10-year period, did not demonstrate a correlation between platelet count and the risk of haemorrhage.[19] Patient-specific factors, including recent bleeding and recipients of hematopoietic stem cell transplantation, rather than platelet counts were associated with increased risk and severity of bleeding. Counter-intuitively, a study of platelet count recovery following hematopoietic stem cell transplantation reported that most clinically important bleeding events occurred when the morning platelet count was greater than 20 x 10^9/L.[20] Finally, a review of all case reports of severe intracranial hemorrhage from studies of prophylactic platelet transfusions found no association between the occurrence of major (intracranial) bleeding and the platelet count just prior to bleeding.[21]

1.1.5 Therapeutic Versus Prophylactic Platelet Transfusion Strategies: Randomized Controlled Trials

Despite the fact that administering prophylactic platelet transfusions to patients with severe thrombocytopenia is a common practice, in several clinical settings this practice is poorly supported by evidence. The best evidence for a prophylactic platelet strategy is in acute leukemia patients.[7] It has been proposed that patients undergoing ASCT and those with chronic, stable thrombocytopenia[9 22] may be effectively managed with a therapeutic transfusion strategy, thus minimizing the need for unnecessary transfusions and their associated risks.

Until recently, the only evidence to support a prophylactic platelet transfusion strategy rather than a therapeutic strategy resulted from three small randomized trials in patients undergoing high dose therapy for acute leukemia in the 1970s.[23-25] In two studies, bleeding events were lower in the patients receiving prophylactic platelet transfusions[23 24] and in two studies, platelet transfusions were reported to be decreased in the patients receiving therapeutic transfusions.[24 25] However, it was difficult to draw any definitive conclusions from these studies as they are older,

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included small numbers of patients who received aspirin therapy as an anti-pyretic and suffered from various methodological limitations.

More recently, two large randomized controlled trials comparing prophylactic and therapeutic platelet transfusion strategies in patients with hematologic malignancies have been published. Firstly, Wandt and colleagues randomized 396 patients undergoing chemotherapy for acute myeloid leukemia or ASCT, to either prophylactic versus therapeutic platelet transfusions. Grade 2 (moderate bleeding not requiring transfusion) or greater bleeding using a modified World Health Organization (WHO) scale occurred in 65 (19%) patients in the prophylactic group and 127 (42%) patients in the therapeutic group ($p<0.0001$).[9] Additionally, there was increase in grade 4 bleeding – 13(7%) versus 4(2%), $p=0.0095$, in patients with acute leukemia in the therapeutic arm. In contrast, in patients undergoing ASCT there was no difference in incidence of grade 3 bleeding or grade 4 bleeding events were observed in either arm. The mean number of platelet transfusions was reduced by 33.5%, ($p<0.0001$) in the therapeutic arm. The authors concluded that prophylactic platelet transfusions should remain the standard of care for patients undergoing treatment for acute leukemia, but a therapeutic strategy could be possibly adopted for patients undergoing ASCT.

Similarly, the TOPPS investigators[7] randomized patients with a variety of hematologic malignancies undergoing chemotherapy, autologous or allogeneic stem cell transplantation to either a prophylactic or therapeutic platelet transfusion strategy. The primary end point, WHO grade 2 bleeding or greater, occurred in 151 (50%) patients in the therapeutic group and 128 (43%) patients in the prophylactic group, ($p=0.06$ for non-inferiority). In a predefined subgroup analysis of patients undergoing ASCT, there was no difference in grade 2 bleeding or higher between the groups – 99/210 (47%) patients in the therapeutic group versus 95/210 (45%) patients in the prophylactic group. For the entire study population, fewer patients in the therapeutic group received platelet transfusions – 176 (59%) versus 266 (89%), $p<0.001$. The authors concluded that prophylactic platelet transfusions should remain the standard of care, but identified that a therapeutic strategy in the ASCT setting warrants further investigation. It is notable that neither the Wandt et al. nor the TOPPS trial were adequately powered to evaluate bleeding risk in the ASCT setting.

1.1.6 Are Platelet Transfusions Harmful?

Among blood products, platelets are associated with the highest risk of transfusion-related infectious and non-infectious complications.[10-13] Some complications associated with platelet transfusions include fevers, rigors, acute lung injury, volume overload, hemolysis, platelet refractoriness, bacterial contamination, and rarely, viral transmission. Though some of these reactions are mild, they often require discontinuation of the transfusion and another transfusion at a later time. This adds stress to the limited platelet inventory, and can also increase patient length of stay, and increase patient anxiety. There is also an emerging body of literature that suggests that transfusions may modulate immunologic function and adversely affect treatment outcome in hematologic malignancies. In a study of acute leukemia patients, increased platelet transfusions during induction was associated with decreased survival[26] and we have recently demonstrated an association between transplant-related morbidity and mortality with the number of platelet transfusions.[6]

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1.1.7 Therapeutic Versus Prophylactic Platelet Transfusion Strategies In Patients Undergoing Autologous Hematopoietic Stem Cell Transplantation

As described above, the results of two recent randomized controlled trials lead us to question the value of prophylactic platelet transfusions in patients undergoing ASCT. Additional evidence for the efficacy of a therapeutic platelet transfusion strategy in this patient group was reported by Wandt et al.[8] They instituted a therapeutic platelet transfusion strategy in consecutive, clinically stable patients undergoing ASCT. Bleeding events were observed in only 26 of the 140 (19%) transplants. The maximum severity was WHO grade 2, with no grade 3 or 4 bleeding. Notably, 47% of high-dose melphalan transplants for multiple myeloma (the most common indication for ASCT) were performed without any platelet transfusions and platelet use was decreased by 53%.

Despite the results of these studies, the Canadian ASCT community remains reluctant to embrace and adopt the use of therapeutic platelet strategy in the ASCT setting. At the same, there is an increasing concern that prophylactic platelet transfusions may not be warranted in all patients.

1.1.8 Tranexamic Acid: An Alternative Prophylactic Strategy

Tranexamic Acid, an antifibrinolytic agent, is a synthetic analog of the amino acid lysine and competitively inhibits the activation of plasminogen to plasmin, thereby reducing the degradation of fibrin, a protein that forms the framework of blood clots. It has been extensively studied in surgical settings where it has been shown to consistently reduce bleeding and transfusion needs.[27-32] Further, it is commonly and safely employed (Table 2) in the management of patients with bleeding disorders such as hemophilia and von Willebrand Disease.[33 34] As some patient groups (e.g. those undergoing induction therapy for acute leukemia) appear to be at higher risk for clinically relevant bleeding, efforts are shifting to try and identify strategies to reduce the risk of bleeding while minimizing patient exposure to blood products. Consequently, there has been interest in its prophylactic use in patients with hematologic malignancies in the context of hypoproliferative thrombocytopenia to prevent bleeding.[15 16]

Taken together, a strategy using prophylactic Tranexamic Acid with therapeutic platelet transfusions can be considered a potential substitute for a strategy of prophylactic platelet transfusions in patients at risk for bleeding.

1.1.9 Assessment of bleeding and quality of life associated with thrombocytopenia in patients undergoing Autologous Hematopoietic Stem Cell Transplantation

Bleeding has been the primary outcome of all the large randomized controlled trials assessing platelet transfusions in patients with hematologic malignancies.[2 4] Almost all these trials have used bleeding scores based on the World Health Organization bleeding score, which classifies bleeding into 4 grades: 1 – mild; 2 – moderate bleeding not requiring red cell transfusions; 3 – moderate to severe bleeding requiring red blood cell transfusion; 4 – life or limb- threatening bleeding.[35] However, the WHO bleeding score has definite limitations including the lack of precise definitions for each bleeding grade and the lack of formal validation.[36 37] Grade 2 bleeding or greater bleeding has been used as the primary outcome in most clinical trials, primarily due to rarity of grade 3 and 4 bleeding. The lack of standardization of bleeding when

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using the WHO bleeding score has resulted in variation in the type and amount of bleeding reported in clinical trials.[38] Additionally, the validity of grade 2 bleeding as the primary outcome measure is problematic as grade 2 bleeding does not predict more severe grade 3 or 4 bleeding, and has never been shown to predict mortality or major morbidity, or be associated with changes in Quality of Life outcomes.[36 39] To address some of these shortcomings in the assessment of bleeding, Webert et al. used measurement theory to develop a validated and reliable bleeding score in patients with hematological malignancies.[40] Outcomes beyond bleeding also need to be considered in clinical trials evaluating platelet transfusions or alternative strategies to prevent bleeding in patients with hematologic malignancies.

Although the rarity of mortality directly related to bleeding precludes its use as a primary outcome in platelet transfusion studies, Quality of Life is an important outcome that assesses the impact of morbidity related both to bleeding and adverse outcomes related to transfusions or medications.[41 42] Ideally, this would be done using both general Quality of Life scales such as the EQ-5D[43] and disease specific scales for thrombocytopenia such as the FACT – thrombocytopenia 18. [44]

1.1.10 Patient and Caregiver Engagement in Clinical Trial Design

Patient and/or informal caregiver's perspective(s) are rarely considered in clinical trials where health care professionals independently determine clinical endpoints. For instance, what degree of bleeding is important from patient's perspective? Are there psychosocial or anxiety concerns that relate to thrombocytopenia? Which endpoint(s) are most pertinent from the patient's perspective? As championed by the Patient-Centered Outcomes Research Institute (PCORI)[45], there has been increasing interest and efforts to engage patients and caregivers to design clinical trials that are relevant and meaningful to the patient. To our knowledge, this has never been studied within the context of bleeding prevention strategies in patients receiving ASCT.

1.1.11 Summary: The Importance of the Problem

It is routine clinical practice to administer prophylactic platelets to prevent bleeding in patients undergoing ASCT. However, the true benefit of prophylactic transfusion to prevent bleeding is unknown. Sub-group analyses from of three recent studies suggest that this population is at low risk for clinically relevant bleeding[7-9] and that the number of platelet transfusions can be significantly reduced by adopting a therapeutic transfusion strategy. This approach has not been accepted in practice due to ongoing concerns of bleeding risk.

Platelet transfusions are not benign. Inherent risks include fever, rigors, hemolysis, acute lung injury, transfusion associated circulatory overload, bacterial and rarely, viral, transmission.10-13 The routine use of frequent platelet transfusions may also increase the risk for alloimmune refractoriness, which may increase the difficulty in treating or preventing bleeding complications. The immune-modulatory effect of platelets may result increase post-transplant toxicity and increase the risk of tumour progression.[6,26] Platelets, in particular single-donor platelets are often in short supply due to reliance on volunteer donation with a shelf-life of only 5 days.[46] Finally, the impact of prophylactic platelet transfusions on the patient's quality of life is largely unknown.

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In patients undergoing ASCT, an alternative approach to prophylactic platelet transfusions to prevent bleeding is to administer prophylactic Tranexamic Acid. Tranexamic Acid is safe, extensively used to prevent bleeding and reduces red cell transfusions in many clinical settings. In contrast to a solely therapeutic platelet transfusion strategy, this cautious approach has the potential to both minimize platelet use and provide this vulnerable population with a safe and effective prophylactic strategy.

In summary, there is a need to reduce the use of unnecessary platelet transfusions and Tranexamic Acid represents a transfusion-free alternative to prevent bleeding in recipients of ASCT.

1.2 Objectives and Hypothesis

We hypothesize that in patients undergoing autologous hematopoietic stem cell transplantation (ASCT), a strategy of prophylactic Tranexamic Acid with therapeutic platelet transfusions for bleeding 1) is safe, 2) improves quality of life, and 3) improves economic outcomes as compared to prophylactic platelet transfusions.

1.3 Trial Overview and Design

PATH is an open-labeled multi-center pilot feasibility parallel-arm 1:1 randomized controlled trial, where participants will be stratified by centre and disease (either myeloma or other hematologic malignancy). We will recruit patients over a 2 year period and follow each participant for a minimum of 30 days.

PATH has been funded by a peer reviewed grant by Canadian Institutes of Health Transitional Open Grant 2014-2015 (RN260949 - 342593) and is registered on the National Institute of Health, Clinicaltrials.gov registry (NCT02650791).

METHODS AND ANALYSIS

Methods and Analysis: Participants, Interventions and Outcomes

2.1 *Study Setting*

PATH will be carried out at 3-4 tertiary Adult Hematopoietic Stem cell transplant centres in Canada.

2.2 Eligibility criteria

Recipients of ASCT should be screened for study eligibility prior to initiation of conditioning chemotherapy and /or radiotherapy. Screening should occur, ideally in a dedicated outpatient clinic prior to hospital admission for ASCT. Inclusion and Exclusion criteria must be satisfied prior to randomization as outlined in Section 2.2.1 and 2.2.2. Randomization will be performed

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on day 0 of the ASCT. Verification that patients still meet all inclusion and exclusion criteria will occur prior to patients being randomized.

2.2.1 Inclusion Criteria

1. Adults 18 years or older undergoing ASCT for a hematologic malignancy
2. Patients providing written informed consent prior to starting transplantation

2.2.2 Exclusion Criteria

1. A previous WHO grade 3 or 4 bleeding event
2. A WHO grade 2 bleeding event within the past year
3. A previous or current thrombotic event defined as a pulmonary embolism, deep vein thrombosis, cerebral thrombosis
4. Active angina (chest pain of presumed cardiac origin either at rest or with activity)
5. Current or previous (within 2 weeks) urinary tract bleeding
6. An inherited hemostatic or thrombotic disorder
7. Coagulopathy defined as a prothrombin time or activated partial thromboplastin time more than 1.5 times the upper limit of normal or fibrinogen less than 2 g/L
8. A requirement for anticoagulant or antiplatelet drugs
9. Previously documented history of refractoriness to platelet transfusion secondary to HLA antibodies
10. Significant renal impairment (creatinine more than 1.5 times the upper limit of normal)
11. Pregnant or breast-feeding
12. Unwilling or unable to provide informed consent
13. Participant has known history of subarachnoid hemorrhage
14. Participant has acquired disturbances to his/her colour vision
15. Participant has known sensitivity or allergy to Tranexamic Acid or any of its ingredients
16. The current use of Oral Contraceptive Pill (Birth Control Pill), Hormonal Contraceptives or Hormone Replacement Therapy.

The use of any other concomitant medications would be at the discretion of the treating physician and his/her team.

2.3 Interventions

All patients undergoing ASCT have daily morning laboratory investigations, including a complete blood count (CBC), performed as part of standard care. We will randomize patients to one of the following bleeding prevention strategies from the day of stem cell infusion (day 0) until platelet engraftment (defined as the first of two consecutive measured platelet counts on different days that are greater than 20 x 10^9/L and increasing in the absence of a platelet transfusion for three consecutive days), or day 30 post ASCT, whichever comes first):

2.3.1 Control Arm: Prophylactic Platelet Transfusion Strategy

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Patients allocated to the prophylactic platelet transfusion group will receive a platelet transfusion when the measured platelet count is less than 10 x 10^9/L.

2.3.2 Experimental Arm: Prophylactic Tranexamic Acid Strategy

Patients allocated to the prophylactic Tranexamic Acid group will receive a standardized routine oral dose of Tranexamic Acid 1 gram three times daily. Tranexamic Acid will start when Platelet count is less than 50 x 10^9/L and continue until platelet engraftment. Patients in this group will not receive routine prophylactic platelet transfusions.

This is not a blinded study. All patients will have their platelet count checked daily or per institutional policy until platelet engraftment. *All patients in both study arms will receive therapeutic platelet transfusions to treat clinically relevant bleeding, defined as World Health Organization (WHO) bleeding of grade 2 or greater.* The WHO grading system is the most commonly used tool in the assessment of bleeding events in platelet transfusion trials.[38] In this system, bleeding episodes are categorized as grade 1 (mild), grade 2 (moderate; red cell transfusion no needed immediately), grade 3 (severe; requiring red cell transfusion within 24 hours), and grade 4 (debilitating or life-threatening; see Table 3).[35] Further, we will also assess bleeding using the Bleeding Severity Measurement Scale.[40]

2.3.3 Therapeutic Platelet Transfusions

All patients may receive therapeutic platelet transfusions for grade 2 bleeding or greater regardless of the platelet count. Therapeutic platelet transfusions can also be given to patients who become clinically unstable, defined as the presence of fever, active infection, or hypotension, and those who require an invasive procedure. Therapeutic platelet transfusions may be administered at any time at the clinician's discretion and the rationale will be recorded. The type of platelet product will follow local institutional practices.

2.3.4 Source of Progenitor cells, Conditioning Regimen and Supportive Care

For all patients, the choice of progenitor cells and conditioning regimen will be determined by the centre and by availability. Similarly, the supportive care strategy will be determined by local institutional policy. This will include, but not limited to the use of antibiotics, analgesia, IV fluids, growth factors and other blood products (not including platelets).

2.4 Outcomes

2.4.1 Primary Outcome (Feasibility)

The primary outcomes of this feasibility trial will be:

1. Enrolment,
2. Number of off-protocol platelet transfusions, and
3. Total number of platelet transfusion per group.
4. Adherence to Tranexamic Acid use

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We will evaluate feasibility by:

1. Recruitment of an average of 2 patients per month per site,
2. Fewer than 10% off-protocol transfusions in each arm, and
3. An absolute reduction of 25% in the total number of platelet transfusions in the Tranexamic Acid arm.
4. Adherence to Tranexamic Acid use. Adherence to Tranexamic Acid use will be defined as follows: Excellent (≥90% consumed), Acceptable (between 75% and 90% consumed), Poor (≤75% consumed). We anticipate Acceptable to Excellent adherence given that study participants will be cared for in an inpatient setting.

During the feasibility trial we will identify any logistical issues related to protocol implementation, randomization strategy or data collection. Furthermore, we will define the sample size required for the definitive trial.

2.4.2 Secondary Outcomes (Clinical)

The secondary outcomes of this trial will be:

1. WHO bleeding events of grade 2 or higher[35]
2. WHO bleeding events of grade 3 or 4[35]
3. Time from randomization to bleeding of WHO grade 2 or higher[35]
4. Number of days with bleeding of WHO grade 2 or higher
5. Bleeding Severity Measurement Scale (BSMS; Table 5)[40] bleeding events of grade 2.
   - Previous studies have used the WHO bleeding scale and have reported substantial inter-observer variability in scoring.[46] Hence, we have elected to use a validated score that has been shown to minimize this variability, in addition to the WHO scale in order to facilitate comparison with other large clinical trials
6. Number of platelet transfusions
7. Number of red cell transfusions:
8. Time to platelet count recovery
9. Number of days with platelet count < 10 x 10^9/L
10. Length of hospital stay:
11. Number and type of adverse transfusion reactions
12. Bearman toxicity score (Table 6)[47]:
13. Incidence of infections at Day 30 following ASCT:
    - Clinically important infections will be ascertained using Centre for Disease Control criteria where grade 4 and 5 infections will be recorded
14. Mortality at Day 30
15. Quality of Life measures: FACT-Thrombocytopenia 18 (Table 7)[44], FACT-BMT (Table 8)[48], GAD-7 (Table 9)[49] and EQ-5D (Table 10)[43]
16. Economic Analyses: incremental cost effectiveness ratios

2.5 Participant timeline

All patients will be followed for 30 days post ASCT. The assigned treatment protocol will be applied from Day 0 of ASCT to platelet engraftment or Day 30, whichever comes first. Assessments of clinical outcomes will occur as detailed in Table 4 until Day30. A detailed

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review of the patient record, laboratory and diagnostic tests will be included during the hospitalization. Research staff will follow all patients daily for the duration of the study period. Participants will be asked to report any possible adverse events immediately.

Adherence to protocol will be appraised by: 1) Nursing documentation in an inpatient setting, and 2) Self-reported Medication Adherence Form in an outpatient setting.

Patients will have their blood counts measured daily or as per institutional policy while on study. More frequent monitoring may be performed at the discretion of the treating physician.

2.6 Sample Size

As a pilot trial, the primary consideration for the sample size is the ability inform the feasibility of a full scale study. We propose a sample size of 50 adults in each treatment group for a total sample size of 100, while stratifying for participants with either myeloma or other hematologic malignancy.

2.7 Recruitment

Each site performs approximately 60 ASCT per year. Importantly, there is already an infrastructure and system in place for participating sites given that there are participating in an ongoing red cell transfusion trigger study in patients receiving a hematopoietic stem cell transplantation. Conservatively, we aim to recruit 2 patients per month at each participating site.

Methods and Analysis: Assignment of Interventions

3.1 Allocation (sequence generation, allocation concealment mechanism) and Implementation

Patients will be stratified by centre and disease (multiple myeloma versus other hematologic malignancies) given that the underlying disease may affect the bleeding risk and the most common indication for ASCT is multiple myeloma.

Further, they will then be assigned either of the transfusion strategy by block randomization to optimize balance between the 2 treatment arms. The randomization sequence will be determined by the Ottawa Methods Centre (Ottawa Hospital Research Institute) generated by computer-generated random numbers where random blocks of 2 and 4 for each participating centre will help facilitate balance.

The Ottawa Methods Centre at the Ottawa Hospital Research Institute will design and maintain web based randomization forms. The forms will contain a check list of eligibility criteria as described in Sections 2.2.1 and 2.2.2. The local investigator and/or designate will “check-off” and acknowledge patient eligibility. If all criteria are met, then randomization will be completed, and the site will be informed of the study arm assigned by email. The recipient will be considered enrolled in the trial at the time of consent.

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Selection bias will be minimized by random allocation to treatment groups and by allocation concealment. Randomization of study participants is a valid and justified method to protect against selection biases. Similarly, co-intervention and confounding would be minimized by the randomized design. The web-based computerized randomization system as described above will be used to ensure the participating centre and individuals remain unaware of the randomization sequence. Concealment of randomization prevents selection bias by ensuring that the participating centres and individuals remain unaware of the randomization sequence. Medical and research staff, and investigators, will be blinded to randomization scheme.

3.2 Blinding (masking)

An open-label design is more prone to ascertainment bias than a double blind trial. However, this should not affect the feasibility outcomes. Moreover, it would be impractical to blind participants and health care professionals to the assigned bleeding prevention strategy. Firstly, a placebo transfusion is not feasible as blinding the treating physicians would compromise safety in making clinical decisions about platelet transfusions in circumstances associated with an increased risk of bleeding. As such, a placebo medication would be impractical given that it would then be then clear which arm is receiving the prophylactic platelet transfusion strategy.

Importantly, recent clinical trials of platelet dose that have attempted to blind subjects and physicians have not been successful as the patients and clinicians were aware of allocation based on the platelet counts and the size of the platelet product.[2] Further, the standard of care requires daily knowledge of platelet count to ensure participants' overall care and safety. We will further reduce ascertainment bias by objectively grading bleeding events using the WHO and BSMS bleeding score.

Methods and Analysis: Data Collection, Management and Analysis

4.1 Data Collection methods

Information will be collected and recorded on Case Report Forms (CRF). These will be completed at study entry (registration and randomization), Day 0 (first day of stem cell infusion), and on an on-going basis until Day 30 post ASCT (or until time of death, whichever is sooner). Copies of the completed CRFs are to be submitted to the Project Management Office within 30 days of Day 0 and Day 30. The original CRFs and Questionnaires will sent to the coordinating centre. Source documentation and copies of CRFs and Questionnaires will be stored at each site.

4.2 Data management

The Ottawa Methods Centre will perform the randomization, data collection and statistical support while the multi-Centre coordinator will oversee management, site monitoring, administration and meeting support. A centralized database will be utilized and housed on a secure server with daily backup. The Multi-centre Coordinator will also communicate with data management and clinical research personnel in each of the participating institutions.

4.3 Statistical methods

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Binary/categorical endpoints will be compared between treatment groups using logistic regression. Both an "intention-to-treat" and on-protocol analysis will be performed. "Intention to treat" analysis will be supplemented by a sensitivity analysis that excludes patients who were non-compliant or loss to follow-up.

Where appropriate, analyses will employ a 2-tailed test for significance to account for the possibility that either treatment arm may be beneficial. Analysis of time-to-failure endpoints will make use of Kaplan-Meier estimates, log-rank tests, and Cox proportional hazards models as appropriate. Binary and categorical endpoints will be compared between treatment groups using logistic regression. The results for each of the endpoints will be summarized using significance tests at level of 0.05 and 95 percent confidence intervals. Analysis of secondary endpoints will be considered exploratory and hypothesis generating.

We will also perform recurrent event analysis for bleeding events as proposed by Cook et al..[50 51] Quality of Life (QOL) data will be summarized using a combination of descriptive statistics and side-by-side box plots showing distributions of scores over time. A further analysis across time points will be done using repeated-measures ANOVA and any transformation to the raw data when statistical appropriate.

All data will be analyzed centrally through the Clinical Epidemiology Program and Centre for Transfusion Research in Ottawa.

Methods and Analysis: Monitoring

5.1 Data Monitoring

The Multi-Centre Coordinator will review the protocol and CRFs with the investigator and study staff before study initiation at the site initiation visit or the investigator's meeting. A monitor will visit sites as needed throughout the duration of the study to verify the quality of data and to ensure the standards of Good Clinical Practice are being met. A monitoring plan will be developed and adhered to for the duration of the study.

During the course of the study, an independent Data Safety Monitoring Board (DSMB) will set up to review efficacy and safety data. The DSMB will consist to a Chair and 2 members. The members will have expertise in Transfusion Medicine, ASCT and Clinical Trials. The DSMB will convene after each 25 patients that are enrolled or after 6months, whichever comes first. Additional meetings/conferences calls will be conducted as necessary. The DSMB will use their experience in reviewing the data submitted to them. There will not be a formal stopping rule; the DSMB will use their experience and expertise to advise the PATH Steering Committee on the prudence of stopping the trial early due to safety concerns.

5.2 Harms

All participants are to be assessed for adverse events according to local institutional practice following standard ASCT except where additional assessment is required per protocol. Source

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documentation of adverse events should be according to institutional practice, except in cases where additional information is required to be documented by the protocol.

5.2.1 Adverse events reporting

Adverse events will be reported in the Data Collection Forms on both study arms as follows:

1. Adverse event reporting should begin on the day 0 of ASCT.
2. All adverse events of grade 3 or greater and serious adverse events will be recorded up to platelet engraftment or Day30, whichever comes first.
3. The start date of each adverse event (that meets the criteria for recording) will be recorded in the "Adverse Event Data Collection" form. The start date is defined as the date the adverse event first meets the criteria for grade 3 or greater. Stop dates do not need to be recorded unless the event is a serious adverse event (SAE) meeting the criteria for expedited reporting.
4. Abnormal laboratory results do not need to be recorded unless considered by the investigator to be relevant in terms of subject or trial safety (or in relation to a serious adverse event that is being reported). Complete Blood Counts (includes a White cell count, Hemoglobin and Platelet) are performed and reviewed during ASCT as part of routine clinical care. These values are expected to decrease as a direct consequence of the transplant procedure, which is unrelated to the red cell transfusion trigger. Consequently, we will not report any low white cell count, hemoglobin or platelet values as an adverse event**,** unless the decrease in these values is directly attributed to the Tranxaemic Acid or platelet transfusion. We will document all platelet values as this is required to establish when a platelet transfusion should occur.

5.2.2 Expedited SAE Reporting

Expedited SAE reporting are those that are deemed *unexpected* (not consistent with product information or labeling) and *related / possibly related* to the study intervention) will be faxed by the PATH Coordinating Centre to the Office of Clinical Trials, Health Canada using a) Adverse Drug Reactions (ADRs) for Clinical Trials Expedited Reporting Summary Form and b) Council for International Organizations of Medical Sciences -CIOMS form) within the following timeframes:

1. where it is neither fatal nor life-threatening, within 15 days after becoming aware of the information;
2. where it is fatal or life-threatening, immediately where possible and, in any event, within 7 days after becoming aware of the information; and
3. within 8 days after having informed Health Canada of the ADR, submit as complete a report as possible which includes an assessment of the importance and implication of any findings. (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta_post_approval-eng.php#adr)

In the case of an Expedited SAE, the PATH SAE form should be forwarded to the Central Coordinator as soon as possible after the site Research Coordinator learns of the event. Ideally,

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the Central Coordinating Centre should be apprised within 24 hours of the event. This requirement is applicable from the day of ASCT up to the end of study follow-up (either Platelet engraftment or Day 30 post-ASCT, whichever comes first).

All fields in the trial-specific SAE form will be completed. The local investigator will review, sign and date the SAE form for confirmation of its accuracy. All Institutional Review Boards (IRB) engaged in the PATH study will be informed of Expedited SAEs by the respective Site Coordinator (once the Multi-centre Coordinator has informed the site). The Multi-centre Coordinator may require further information from the site research team in order to complete the submission to Health Canada. Site research teams are requested to provide such requested information in a timely fashion.

The Study Chair and/or Study Steering Committee will review all SAE's received from the sites. If an SAE is confirmed, a document summarizing the SAE will be distributed to participating sites. Sites will follow the guidelines of their local IRB with respect to the submission of SAE's that occur at the site as well as SAE Notifications.

5.2.3 Grading of Adverse Events

The NCI Common Toxicity Criteria (CTCAE) Version 4 will be used to grade adverse events that recipients experience. A copy of version 4 of the CTCAE is available from the CTEP home page [http://ctep.info.nih.gov]

5.2.4 Reporting of Deaths

All deaths must be reported to the Project Management Office within 24 hours of the site's knowledge of the death. This requirement is applicable from the 1st day of HSCT to the end of study follow-up (Day 30 post-ASCT). Death is considered a separate SAE from the SAE that precedes the death (i.e. the SAE leading to the death). A separate Death form must be completed in addition to the SAE form.

5.3 Auditing

The investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the CRF entries. No information in these records about the identity of the patients will leave the study centre. Monitoring standards require verification of the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of all adverse events and outcomes required as per protocol. The investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB review and regulatory inspections(s), providing direct access to source data/documents.

ETHICS AND DISSEMINATION

6.1 Research ethics approval

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This study will be undertaken at a site only after IRB has given full approval of the final protocol, amendments (if any), the informed consent form(s), applicable recruiting materials, and the study management center has received a copy of this approval. This approval letter must be dated and must clearly identify the documents being approved. The study management center will require a copy of all IRB documents.

6.2 Protocol amendments

Any protocol amendments will be approved by the Steering Committee and communicated electronically to site investigators and research staff. In turn, the amended protocol will be forwarded to respective site IRBs for review. Health Canada and the online trial registry will be accordingly updated.

6.3 Consent or assent

The recipient and/or the recipient's legally authorized guardian must acknowledge in writing (consent) to become a study subject on the PATH study. Consent will be obtained jointly by the most responsible health care provider (local investigator or co-investigator) and the local research coordinator.

6.4 Confidentiality

Case Report Forms will be faxed or mailed to the Multi-Centre Coordinator's Office at registration and at follow-up time points. Data will be identified by an alphanumeric code only. Data will be entered (by staff at the Multi-Centre Coordinator's Office or Data Management Services) into the database. Importantly, source documentation will remain at their respective participating centre's site. The server for the database will be located in the Ottawa Hospital Research Institute under the care of the Methods Centre. Appropriate security measures will be in place such that current Canadian privacy laws are adhered to with respect to security and confidentiality of data, electronic data transmission, data storage and data access. A secure ID and password will be necessary to access the system. Audit trails of entries will be provided. The Project Manager and delegate will be the only individuals that can edit data. Records will be retained for a period of 25 years as per Health Canada regulations. After 25 years, all study records will be destroyed according to local policy. If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility.

Sites will track enrolment on a log where they will record the following information: patient name, hospital number, contact information, unique study number (randomization number), and study arm assigned. This log will not leave the site and will not be sent to the coordinating center. The unique study number will be used to identify all CRFs (paper) from the site to the Multi-centre Coordinator's Office. The unique study number should be used regarding any other communication between the site and the Multi-centre Coordinator's Office.

6.5 Declaration of interests

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The authors and investigators have no relevant conflicts of interests.

6.6 Access to data

The Multi-Centre Coordinator's Office (and delegate) will be the only individuals who have authorization to transfer data to the statistician for study analysis.

6.7 Ancillary and post-trial care

There will be no specific post-trial care, where medical care will follow local institutional practices. In the event of a study-related injury or illness, the participant will be provided with appropriate medical treatment and care. Financial compensation for lost wages, disability or discomfort due to an injury or illness will not be available. The legal rights of the participant will not be waived as a result of participation in the PATH. The investigators and their respective institutions will still have their legal and professional responsibilities.

6.8 Dissemination policy

Knowledge translation activities will take place throughout the duration of the study and will include clinical rounds, presentations, research team presentations at conferences, and web-based disseminations. The project is registered with ClinicalTrials.gov. Scholarly articles will be submitted to relevant journals with open access publication. At the time or writing, there is no specific plan(s) to grant public access to the full protocol, participant-level dataset, or statistical code.

ADMINISTRATIVE INFORMATION

Steering Committee

The interdisciplinary research team is composed of experienced researchers and clinicians with expertise in Stem cell transplantation, psychology and quality of life measures in transplant, transfusion medicine as well as clinical trials. The principal investigators and the co-investigators will serve as the steering committee. Independently and collectively the investigators have a wide range of expertise including transfusion medicine (AT, DS), transplantation (CB, DA, MS, DS, JT), malignant hematology (JT, DS, MS), clinical psychology and quality of life (SB), clinical trials (AT, DAF, JT, DS, KT, CB), epidemiology (DAF, AT, JT, DS, KT, CB) and economic analyses (KT).

Trial Sponsor

The PATH study is sponsored by The Ottawa Hospital Research Institute, 725 Parkdale Ave. Ottawa, Ontario, Canada, K1Y 4E9.

DISCUSSION

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Prophylactic platelet transfusions are commonly prescribed in patients undergoing ASCT to prevent bleeding based on daily measured platelet threshold (commonly < 10 x 10^9/L). However, observational studies suggest that the platelet number does not correlate with clinical significant bleeding. Moreover, recent randomized studies suggest that prophylactic transfusions may not be necessary in patients receiving ASCT. However, ASCT clinicians remain uncomfortable not providing prophylactic platelets in the presence of thrombocytopenia. The PATH pilot study will "bridge this gap" with the use of prophylactic tranexamic acid instead of prophylactic platelet transfusions.

There are several innovative features of the PATH pilot study design. Firstly, investigations will remain blinded to the data collected in this pilot study. The data will be reviewed in aggregate by the investigators while unblinded data is available to the DSMB. In this way, the patients enrolled in this pilot study can be part of the eventual sample size for the definitive phase III study. Secondly, the collection of patient reported outcomes/quality of life data is unique in clinical trials in platelet transfusions. Finally, we intend to engage patients and caregivers to better appreciate their preferences for a primary endpoint, in designing a Phase III study.

Given the resource utilization and high rate of adverse outcomes in HSCT, our study will provide the framework for better understanding the optimal use of platelet transfusions in patients receiving an ASCT. In this pilot study, we aim to determine the feasibility and logistics of conducting a multicenter trial and determine clinical outcome rates in order to plan and execute a prospective definitive randomized study.

TRIAL STATUS – MILESTONES AND CURRENT STATUS

This trial was conceived and designed in the autumn of 2014. Peer reviewed funding through the Canadian Institute of Health Research Transitional Operation Grant Competition 2014-2015 was sought in 02 March 2015 and successfully obtained on April 2015. Developments in protocol, randomization scheme, data management, case report forms, study monitoring and DSMB setup occurred between April and Dec 2015. The trial was registered on clinicaltrials.gov on 06 Jan 2016. Research Ethics Board approval at the Ottawa Health Science Network Research Ethics Board took place on 26 May 2016. We in the process of finalizing an electronic version of our case report forms and trial database management systems. We anticipate that the study will begin enrollment in Ottawa in August 2016 while HSCT centres in Calgary, Hamilton, London and Saskatoon have been approached for involvement.

COMPETING INTERESTS

The authors declare that they have no competing interests. The sponsors had no role in study design and preparation of the article, conduct of the study, and in the decision to submit the paper for publication.

ABBREVIATIONS

ADR	Adverse Drug Reactions
ASCT	Autologous Stem Cell Transplantation

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BSMS	Bleeding Severity Measurement Scale
CRF	Case Report Forms
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
IRB	Institutional Review Board
PCORI	Patient-Centered Outcomes Research Institute
PATH	Platelet Transfusions in Hematopoietic Stem cell Transplantation
SAE	Severe Adverse Event
WHO	World Health Organization

AUTHOR'S CONTRIBUTIONS

All listed authors (JT, DA, SB, CB, DF, MS, DS, KT and AT) were equally involved in the design of the study and original grant submission to the Canadian Institute of Health Research. JT is the principal investigator involved in the protocol development, "write-up" of this manuscript, execution and "day to day" management of this study. Equal input was received from all other listed authors with respect to the above activities. All authors read and approved the final manuscript.

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REFERENCES

1. Paulsen K. Canadian Blood and Marrow Transplant Group Registry. In: Sheppard D, ed., 2015.
2. Estcourt L, Stanworth S, Doree C, et al. Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation. Cochrane Database Syst Rev 2012;**5**:CD004269.
3. Kaufman RM, Djulbegovic B, Gernsheimer T, et al. Platelet transfusion: a clinical practice guideline from the AABB. Ann Intern Med 2015;**162**(3):205-13.
4. Kumar A, Mhaskar R, Grossman BJ, et al. Platelet transfusion: a systematic review of the clinical evidence. Transfusion 2015;**55**(5):1116-27; quiz 15.
5. Nahirniak S, Slichter SJ, Tanael S, et al. Guidance on platelet transfusion for patients with hypoproliferative thrombocytopenia. Transfus Med Rev 2015;**29**(1):3-13.
6. Christou G, Kekre N, Petrcich W, et al. Impact of platelet transfusion on toxicity and mortality after hematopoietic progenitor cell transplantation. Transfusion 2015;**55**(2):253-8.
7. Stanworth SJ, Estcourt LJ, Powter G, et al. A no-prophylaxis platelet-transfusion strategy for hematologic cancers. N Engl J Med 2013;**368**(19):1771-80.
8. Wandt H, Schaefer-Eckart K, Frank M, et al. A therapeutic platelet transfusion strategy is safe and feasible in patients after autologous peripheral blood stem cell transplantation. Bone Marrow Transplant 2006;**37**(4):387-92.
9. Wandt H, Schaefer-Eckart K, Wendelin K, et al. Therapeutic platelet transfusion versus routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study. Lancet 2012;**380**(9850):1309-16.
10. Callum JL, Lin Y, Pinkerton PH, et al. *Bloody Easy 3: Blood Transfusions, Blood Alternatives and Transfusion Reactions, A Guide to Transfusion Medicine*. 3rd ed: Orbcon, 2011.
11. Galel SA. Infectious Disease Screening AABB Technical Manual. 18th ed, 2014:179-206.
12. Lin Y, Callum JL, Pinkerton PH. Adverse Reactions. Clinical Guide To Transfusion. 2011 ed, 2013.
13. Mazzei CA, Popovsky M, Kopko PM. Noninfectious Complications of Blood Transfusion In: Fung M, Grossman BJ, Hillyer C, et al., eds. AABB Technical Manual, 2014:665-92.
14. Wardrop D, Estcourt LJ, Brunskill SJ, et al. Antifibrinolytics (lysine analogues) for the prevention of bleeding in patients with haematological disorders. Cochrane Database Syst Rev 2013;**7**:CD009733.
15. Avvisati G, ten Cate JW, Buller HR, et al. Tranexamic acid for control of haemorrhage in acute promyelocytic leukaemia. Lancet 1989;**2**(8655):122-4.
16. Shpilberg O, Blumenthal R, Sofer O, et al. A controlled trial of tranexamic acid therapy for the reduction of bleeding during treatment of acute myeloid leukemia. Leuk Lymphoma 1995;**19**(1-2):141-4.
17. Bredeson C. President of Canadian Blood and Marrow Transplant Group. In: Sheppard D, ed., 2015.
18. Gaydos LA, Freireich EJ, Mantel N. The quantitative relation between platelet count and hemorrhage in patients with acute leukemia. N Engl J Med 1962;**266**:905-9.
19. Friedmann AM, Sengul H, Lehmann H, et al. Do basic laboratory tests or clinical observations predict bleeding in thrombocytopenic oncology patients? A reevaluation of prophylactic platelet transfusions. Transfus Med Rev 2002;**16**(1):34-45.

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20. Bernstein SH, Nademanee AP, Vose JM, et al. A multicenter study of platelet recovery and utilization in patients after myeloablative therapy and hematopoietic stem cell transplantation. Blood 1998;**91**(9):3509-17.
21. Stanworth SJ, Hyde C, Brunskill S, et al. Platelet transfusion prophylaxis for patients with haematological malignancies: where to now? Br J Haematol 2005;**131**(5):588-95.
22. Schiffer CA, Anderson KC, Bennett CL, et al. Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. J Clin Oncol 2001;**19**(5):1519-38.
23. Higby DJ, Cohen E, Holland JF, et al. The prophylactic treatment of thrombocytopenic leukemic patients with platelets: a double blind study. Transfusion 1974;**14**(5):440-6.
24. Murphy S, Litwin S, Herring LM, et al. Indications for platelet transfusion in children with acute leukemia. Am J Hematol 1982;**12**(4):347-56.
25. Solomon J, Bofenkamp T, Fahey JL, et al. Platelet prophylaxis in acute non-lymphoblastic leukaemia. Lancet 1978;**1**(8058):267.
26. Blumberg N, Heal JM, Liesveld JL, et al. Platelet transfusion and survival in adults with acute leukemia. Leukemia 2008;**22**(3):631-5.
27. Eftekharian H, Vahedi R, Karagah T, et al. Effect of tranexamic acid irrigation on perioperative blood loss during orthognathic surgery: a double-blind, randomized controlled clinical trial. J Oral Maxillofac Surg 2015;**73**(1):129-33.
28. Karaaslan F, Karaoglu S, Mermerkaya MU, et al. Reducing blood loss in simultaneous bilateral total knee arthroplasty: combined intravenous-intra-articular tranexamic acid administration. A prospective randomized controlled trial. Knee 2015;**22**(2):131-5.
29. Mirghafourvand M, Mohammad-Alizadeh S, Abbasalizadeh F, et al. The effect of prophylactic intravenous tranexamic acid on blood loss after vaginal delivery in women at low risk of postpartum haemorrhage: a double-blind randomised controlled trial. Aust N Z J Obstet Gynaecol 2015;**55**(1):53-8.
30. Roberts I, Coats T, Edwards P, et al. HALT-IT--tranexamic acid for the treatment of gastrointestinal bleeding: study protocol for a randomised controlled trial. Trials 2014;**15**:450.
31. Sprigg N, Renton CJ, Dineen RA, et al. Tranexamic acid for spontaneous intracerebral hemorrhage: a randomized controlled pilot trial (ISRCTN50867461). J Stroke Cerebrovasc Dis 2014;**23**(6):1312-8.
32. Zehtabchi S, Abdel Baki SG, Falzon L, et al. Tranexamic acid for traumatic brain injury: a systematic review and meta-analysis. Am J Emerg Med 2014;**32**(12):1503-9.
33. National Heart Lung and Blood Institute. The diagnosis, evaluation, and management of von Willebrand disease. NIH publication no 08-5832. Bethesda, MD: U.S. Dept. of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute,, 2007.
34. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. Haemophilia 2013;**19**(1):e1-47.
35. World Health Organization. *WHO handbook for reporting results of cancer treatment*. Geneva: World Health Organization, 1979.
36. Bercovitz RS, O'Brien SH. Measuring bleeding as an outcome in clinical trials of prophylactic platelet transfusions. Hematology Am Soc Hematol Educ Program 2012;**2012**:157-60.

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37. Koreth R, Weinert C, Weisdorf DJ, et al. Measurement of bleeding severity: a critical review. Transfusion 2004;**44**(4):605-17.
38. Estcourt LJ, Heddle N, Kaufman R, et al. The challenges of measuring bleeding outcomes in clinical trials of platelet transfusions. Transfusion 2013;**53**(7):1531-43.
39. Webert K, Cook RJ, Sigouin CS, et al. The risk of bleeding in thrombocytopenic patients with acute myeloid leukemia. Haematologica 2006;**91**(11):1530-7.
40. Webert KE, Arnold DM, Lui Y, et al. A new tool to assess bleeding severity in patients with chemotherapy-induced thrombocytopenia. Transfusion 2012;**52**(11):2466-74; quiz 65.
41. Estcourt LJ, Pinchon D, Symington E, et al. Does bleeding affect patient-reported outcome measures in patients with myelodysplasia or hematologic malignancies: a systematic review. Transfusion 2014;**54**(4):1166-79.
42. Heddle NM, Arnold DM, Webert KE. Time to rethink clinically important outcomes in platelet transfusion trials. Transfusion 2011;**51**(2):430-4.
43. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. Ann Med 2001;**33**(5):337-43.
44. Cella D, Beaumont JL, Webster KA, et al. Measuring the concerns of cancer patients with low platelet counts: the Functional Assessment of Cancer Therapy--thrombocytopenia (FACT-Th) questionnaire. Support Care Cancer 2006;**14**(12):1220-31.
45. Patient-Centered Outcomes Research Institute 2015 [Available from: http://www.pcori.org/.
46. Estcourt LJ, Heddle N, Kaufman R, et al. The challenges of measuring bleeding outcomes in clinical trials of platelet transfusions. Transfusion 2013;**53**(7):1531-43.
47. Bearman SI, Appelbaum FR, Buckner CD, et al. Regimen-related toxicity in patients undergoing bone marrow transplantation. J Clin Oncol 1988;**6**(10):1562-8.
48. McQuellon RP, Russell GB, Cella DF, et al. Quality of life measurement in bone marrow transplantation: development of the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) scale. Bone Marrow Transplant 1997;**19**(4):357-68.
49. Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. Arch Intern Med 2006;**166**(10):1092-7.
50. Cook RJ, Heddle NM, Rebulla P, et al. Methods for the analysis of bleeding outcomes in randomized trials of PLT transfusion triggers. Transfusion 2004;**44**(8):1135-42.
51. Heddle NM, Cook RJ, Tinmouth A, et al. A randomized controlled trial comparing standard- and low-dose strategies for transfusion of platelets (SToP) to patients with thrombocytopenia. Blood 2009;**113**(7):1564-73.

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*Table 1: Platelet Transfusion Risks**

Risk of Event	Event
1 in 20	Febrile non-hemolytic transfusion reaction per pool of platelets
1 in 100	Minor allergic reactions (urticaria)
1 in 300	Febrile non-hemolytic transfusion reaction per unit of RBC (1 'donor exposure')
1 in 700	Transfusion-associated circulatory overload per transfusion episode
1 in 7,000	Delayed hemolytic transfusion reaction
1 in 10,000	Transfusion-related acute lung injury (TRALI)
1 in 10,000	Symptomatic bacterial sepsis per pool of platelets
1 in 40,000	ABO-incompatible transfusion per RBC transfusion episode
1 in 40,000	Serious allergic reaction per unit of component
1 in 60,000	Death from bacterial sepsis per pool of platelets
1 in 153,000**	Transmission of hepatitis B virus per unit of component
1 in 250,000	Symptomatic bacterial sepsis per unit of RBC
1 in 500,000	Death from bacterial sepsis per unit of RBC
< 1 in 1,000,000	Transmission of West Nile Virus
1 in 2,300,000	Transmission of hepatitis C virus per unit of component
1 in 4,000,000	Transmission of Chagas disease per unit of component
1 in 4,300,000	Transmission of HTLV per unit of component
1 in 7,800,000	Transmission of human immunodeficiency virus (HIV) per unit of component

Risk of Event	Event
1 in 100	**Hives** (itchy skin rash)
1 in 300	**Fever**
1 in 700	**Heart failure**
1 in 7,000	Delayed **hemolysis**. Hemolysis is when your red blood cells are destroyed
1 in 10,000	**Lung injury**
1 in 10,000	Symptomatic **bacterial sepsis**, per pool of platelets. **Sepsis** is when you get an infection in your bloodstream or tissue
1 in 40,000	Wrong ABO (blood) group, per unit of red blood cells
1 in 40,000	**Anaphylaxis**, which is an extreme sensitivity to a drug or substance that can result in death
1 in 60,000	Death from **bacterial sepsis**, per pool of platelets
1 in 153,000	**Hepatitis B Virus (HBV)** transmission per unit of component. Hepatitis is an inflammation of the liver. **HBV** is a virus that is spread through contact with infected blood, blood products and body fluids
1 in 250,000	Symptomatic **bacterial sepsis**, per unit of red blood cells
1 in 500,000	Death from **bacterial sepsis**, per unit of red blood cells
< 1 in 1,000,000	Transmission of **West Nile Virus**
1 in 2,300,000	**Hepatitis C Virus (HCV)** transmission, per unit of component. Hepatitis is an inflammation of the liver. **HCV** is a virus that is spread through injection drug use, tattooing, and body piercing
1 in 4,000,000	Transmission of **Chagas Disease**. **Chagas Disease** is a parasite that can be transmitted through transfusion
1 in 4,300,000	**Human T-cell lymphotropic virus (HTLV)** transmission, per unit of component. **HTLV** is a virus that can be transmitted by exposure to blood or sexual contact, and can cause a form of cancer of the blood
1 in 7,800,000	**Human Immunodeficiency Virus (HIV)** transmission, per unit of component. **HIV** is the virus that causes AIDS. HIV attacks the immune system

*http://ibta.ir/en/wp-content/uploads/111_Bloody-Easy_3rd-1.pdf

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*Table 2: Tranexamic Acid Risks**

Adverse Reactions Significant

>10%:

1. Central nervous system: Headache (50%)
2. Gastrointestinal: Abdominal pain (20%)
3. Neuromuscular & skeletal: Back pain (21%), muscle pain (11%)
4. Respiratory: Nasal/sinus symptoms (25%)

1% to 10%:

1. Central nervous system: Fatigue (5%)
2. Hematologic: Anemia (6%)
3. Neuromuscular & skeletal: Arthralgia (7%), muscle cramps/spasms (7%)

All formulations: <1% (Limited to important or life-threatening): Allergic skin reaction, anaphylactic shock, anaphylactoid reactions, cerebral thrombosis, deep vein thrombosis (DVT), diarrhea, dizziness, nausea, pulmonary embolism, renal cortical necrosis, retinal artery/vein obstruction, seizure, ureteral obstruction, visual disturbances (including impaired color vision and loss), vomiting

*http://www.uptodate.com/contents/tranexamic-acid-drug-information?source=preview&search=%2Fcontents%2Fsearch&anchor=F229896&selectedTitle=1~78#F229896

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Table 3: World Health Organization Bleeding Grades

Score	*Bleeding Symptoms*
0	None
1	Petechiae, ecchymosis, occult blood in body secretions, mild vaginal spotting, epistaxis lasting less than 30 minutes
2	Evidence of gross hemorrhage not requiring red cell transfusion transfusion over routine transfusion needs: epistaxis lasting greater than or equal to 30 minutes, hematuria, hematemesis, hematoma, hematoochezia
3	Hemorrhage requiring transfusion of one or more units of red cells within 24 hours
4	Life-threatening hemorrhage, defined as either massive bleeding causing hemodynamic compromise or bleeding into a vital organ (e.g., intracranial, pericardial, or pulmonary hemorrhage) or death.

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Table 4: Schedule of Activities

Type of visit	Screening	Enrollment	Randomization	Week 1	Week 2	Week 3	Week 4
Screening							
Timing of visit		Pre-ASCT*	Day 0				
Confirm eligibility criteria	x	x	x				
Informed Consent	x						
Baseline Characteristics							
Demographic data		x					
Disease, treatment history		x					
ECOG and Karnofsky performance status		x					
Comorbidities		x					
Bleeding history		x					
Bleeding assessment (WHO & BSMS)		x					
Interventions^							
Daily Oral Tranxaemic Acid† or Prophylactic Platelets~				x	x	x	x
Assessments							
Complete Blood Count‡			x	x	x	x	x
Daily bleeding assessments (WHO & BSMS)^			x	x	x	x	x
Bearman Toxicity Scale							x
Daily NCI Toxicity Criteria Assessment for SAEs and AEs				x	x	x	x
Quality of Life Assessments#							
FACT-BMT		x		x	x	x	x
FACT-Thrombocytopenia 18		x		x	x	x	x
EQ-5D		x		x	x	x	x
GAD-7		x		x	x	x	x

** The enrollement visit should occur within 14 days prior to start of conditioning chemotherapy*

‡ Daily or as per institutional policy

^ From Day 0 until platelet engraftment or Day 30, whichever occurs first

† From first day with platelet count < 50 x 10^9 /L until platelet engraftment or Day 30, whichever occurs first

~ Prophylactic platelets to be prescribed as per institutional practice

 # Quality of Life Assessments to be performed once a week ± 2 days

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Table 5: Bleeding Severity Measurement Scale (BSMS)

TABLE 3. The BSMS*

Bleeding grade and classification		Description of bleeding
0. No bleeding		No bleeding.
1. Not clinically significant bleeding	1(a) Trace bleeding	Minimal bleeding or bleeding detectable by laboratory measures only. Bleeding does not have any impact on patient or on the level of care provided to the patient.
	1(b) Mild bleeding	Non–clinically significant bleeding. Bleeding does not have any impact on patient or level of care provided to the patient.
2. Clinically significant bleeding	2(a) Serious bleeding	Bleeding directly resulting in one or more of the following: • Significant pain (requiring medical treatment or intervention) • Need for interventions (including transfusion, surgery, invasive procedures, administration of medication, etc.) • Need for invasive investigations or increased monitoring
	2(b) Serious bleeding causing significant morbidity	Any bleeding meeting one or more of the following criteria: • All central nervous system bleeding • Resulting in hemodynamic instability: – Tachycardia (increase in resting heart rate by at least 20 bpm) *or* – Hypotension (decrease in systolic and/or diastolic BP by at least 20 mmHg) • Resulting in vision loss • Resulting in significant morbidity
	2(c) Fatal bleeding	Any bleeding directly contributing to patient's death

General instructions:

1. In most instances, the scale is meant to document new or ongoing bleeding. For example, a bruise should be documented on its first occurrence. After initial documentation, it should only be documented if it is worsening in severity.
2. The highest scoring bleeding determines the patient's bleeding severity on that day.
3. Sources of information to help document bleeding include the patient (examination, history) and the hospital chart (medications prescribed, investigations ordered, physicians/nurses notes, etc.), and health care providers looking after the patient.
4. Note that an isolated decrease in Hb may not be considered sufficient evidence of a bleed.

* Grade 1 bleeding consists of trace bleeding and mild bleeding and is not clinically significant. Grade 2 bleeding consists of serious bleeding, serious bleeding causing significant morbidity, and fatal bleeding. Grade 2 bleeding is clinically significant.

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Table 6: Bearman Toxicity Grading Scale

	Grade I	Grade II	Grade III
Cardiac toxicity	Mild EKG abnormality, not requiring medical intervention; or noted heart enlargement on chest x-ray with no clinical symptoms	Moderate EKG abnormalities requiring and responding to medical intervention; or requiring continuous monitoring without treatment; or congestive heart failure responsive to digitalis or diuretics	Severe EKG abnormalities with no or only partial response to medical intervention; or heart failure with no or only minor response to medical intervention; or decrease in voltage by more than 50%
Bladder toxicity	Macroscopic hematuria after 2 days from last chemotherapy dose with no subjective symptoms of cystitis and not caused by infection	Macroscopic hematuria after 7 days from last chemotherapy dose not caused by infection; or hematuria after 2 days with subjective symptoms of cystitis not caused by infection	Hemorrhagic cystitis with frank blood, necessitating invasive local intervention with installation of sclerosing agents, nephrostomy or other surgical procedure
Renal toxicity	Increase in creatinine up to twice the baseline value (usually the last recorded before start of conditioning)	Increase in creatinine above twice baseline but not requiring dialysis	Requirement of dialysis
Pulmonary toxicity	Dyspnea without chest x-ray changes not caused by infection or congestive heart failure; or chest x-ray showing isolated infiltrate or mild interstitial changes without symptoms not caused by infection or congestive heart failure	Chest x-ray with extensive localized infiltrate or moderate interstitial changes combined with dyspnea and not caused by infection or CHF; or decrease of PO_2 (> 10% from baseline) but not requiring mechanical ventilation or > 50% O_2 on mask and not caused by infection or CHF	Interstitial changes requiring mechanical ventilatory support or > 50% oxygen on mask and not caused by infection or CHF
Hepatic toxicity	Mild hepatic dysfunction with bilirubin ≥ 2.0 mg/dL and ≤ 6.0 mg/dL or weight gain > 2.5% and < 5% from baseline, of non-cardiac origin; or SGOT increase more than 2-fold but less than 5-fold from lowest preconditioning	Moderate hepatic dysfunction with bilirubin > 6.0 mg/dL and < 20 mg/dL; or SGOT increase > 5-fold from preconditioning; or clinical ascitis or image documented ascitis > 100 mL; or weight gain > 5% from baseline of non-cardiac origin	Severe hepatic dysfunction with bilirubin > 20 mg/dL; or hepatic encephalopathy; or ascitis compromising respiratory function
CNS toxicity	Somnolence but the patient is easily arousable and oriented after arousal	Somnolence with confusion after arousal; or other new objective CNS symptoms with no loss of consciousness not more easily explained by other medication, bleeding or CNS infection	Seizures or coma not explained (documented) by other medication, CNS infection, or bleeding

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Table 7: FACT-Thrombocytopenia-18

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please m☐k this box and go to the*					
GS7	I am satisfied with my sex life	0	1	2	3	4

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

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

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

	ADDITIONAL CONCERNS	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 12	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 15	For women only: I am bothered by vaginal bleeding	0	1	2	3	4

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Table 8: ***FACT-BMT***

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

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

	EMOTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	Not at all	A little bit	Some-what	Quite a bit	Very much
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

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	ADDITIONAL CONCERNS	Not at all	A little bit	Some-what	Quite a bit	Very much
BMT1	I am concerned about keeping my job (include work at home)	0	1	2	3	4
BMT2	I feel distant from other people	0	1	2	3	4
BMT3	I worry that the transplant will not work	0	1	2	3	4
BMT4	The side effects of treatment are worse than I had imagined	0	1	2	3	4
C6	I have a good appetite	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
BMT5	I am able to get around by myself	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
BL4	I am interested in sex	0	1	2	3	4
BMT7	I have concerns about my ability to have children	0	1	2	3	4
BMT8	I have confidence in my nurse(s)	0	1	2	3	4
BMT9	I regret having the bone marrow transplant	0	1	2	3	4
BMT10	I can remember things	0	1	2	3	4
Br1	I am able to concentrate	0	1	2	3	4
BMT11	I have frequent colds/infections	0	1	2	3	4
BMT12	My eyesight is blurry	0	1	2	3	4
BMT13	I am bothered by a change in the way food tastes	0	1	2	3	4
BMT14	I have tremors	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
BMT15	I am bothered by skin problems (e.g., rash, itching)	0	1	2	3	4
BMT16	I have trouble with my bowels	0	1	2	3	4
BMT17	My illness is a personal hardship for my close family members	0	1	2	3	4
BMT18	The cost of my treatment is a burden on me or my family	0	1	2	3	4

Table 9: GAD-7

Generalized Anxiety Disorder 7-item (GAD-7) scale

Over the last 2 weeks, how often have you been bothered by the following problems?	Not at all sure	Several days	Over half the days	Nearly every day
1. Feeling nervous, anxious, or on edge	0	1	2	3
2. Not being able to stop or control worrying	0	1	2	3
3. Worrying too much about different things	0	1	2	3
4. Trouble relaxing	0	1	2	3
5. Being so restless that it's hard to sit still	0	1	2	3
6. Becoming easily annoyed or irritable	0	1	2	3
7. Feeling afraid as if something awful might happen	0	1	2	3
Add the score for each column	+	+	+	
Total Score *(add your column scores)* =				

If you checked off any problems, how difficult have these made it for you to do your work, take care of things at home, or get along with other people?

Not difficult at all _____
Somewhat difficult _____
Very difficult _____
Extremely difficult _____

Source: Spitzer RL, Kroenke K, Williams JBW, Lowe B. A brief measure for assessing generalized anxiety disorder. *Arch Inern Med.* 2006;166:1092-1097.

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Table 10: EQ-5D

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility
- I have no problems in walking about ☐
- I have some problems in walking about ☐
- I am confined to bed ☐

Self-Care
- I have no problems with self-care ☐
- I have some problems washing or dressing myself ☐
- I am unable to wash or dress myself ☐

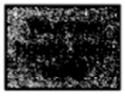
Usual activities *(e.g. work, study, housework, family or leisure activities)*
- I have no problems with performing my usual activities ☐
- I have some problems with performing my usual activities ☐
- I am unable to perform my usual activities ☐

Pain/discomfort
- I have no pain or discomfort ☐
- I have moderate pain or discomfort ☐
- I have extreme pain or discomfort ☐

Anxiety/depression
- I am not anxious or depressed ☐
- I am moderately anxious or depressed ☐
- I am extremely anxious or depressed ☐

To help people say how good or bad a health state is, we have drawn a scale (rather like a thermometer) on which the best state you can imagine is marked 100 and the worst state you can imagine is marked 0.

We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.



Best imaginable health state

100
90
80
70
60
50
40
30
20
10
0

Worst imaginable health state

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	1-24
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 21
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19 - 20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14 & 20

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3 - 8
	6b	Explanation for choice of comparators	6 - 8
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8 - 9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9 - 10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10 - 11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11 - 12 & Table 4

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13 - 14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13- 14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13 -14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14 - 15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14-16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16 & 19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16 & 19

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	17
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	18
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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Rationale and Design of Platelet Transfusions in Hematopoietic Stem cell Transplantation: The PATH Pilot Study

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Rationale and Design of Platelet Transfusions in Hematopoietic Stem cell Transplantation: The PATH Pilot Study

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Abstract

Introduction

In patients with transient thrombocytopenia being treated with high-dose chemotherapy followed by stem cell rescue – Hematopoietic Stem cell Transplantation (HSCT), prophylactic transfusions are standard therapy to prevent bleeding. However, a recent multicenter trial suggests that prophylactic platelet transfusions in HSCT may not be necessary. Additionally, the potential overuse of platelet products places a burden on a scarce health care resource. Moreover, the benefit of prophylactic platelet transfusions to prevent clinically relevant hemorrhage is debatable. Current randomized data compares different thresholds for administering prophylactic platelets or prophylactic vs. therapeutic platelet transfusions. An alternative strategy involves prescribing prophylactic anti-fibrinolytic agents such as tranexamic acid to prevent bleeding.

Methods and Analysis

This report describes the design of an open labelled randomized pilot study comparing the prophylactic use of oral tranexamic acid with platelet transfusions in the setting of autologous HSCT. In 3-5 centres, 100 patients undergoing an Autologous HSCT will be randomly assigned to either a prophylactic tranexamic acid or prophylactic platelets bleeding prevention strategy based daily platelet values up to 30 days post-transplant. The study will stratified by centre and type of transplant. The primary goal is to demonstrate study feasibility while collecting clinical outcomes on 1) WHO and BSMS Bleeding Scales, 2) Transplant Related Mortality, 3) Quality of Life, 4) Length of Hospital Stay, 5) ICU Admission rates, 6) Bearman Toxicity scores, 7) Incidence of Infections, 8) Transfusion requirements, 9) Adverse reactions and 10) Economic Analyses

Ethics and Dissemination

This study is funded by a peer-reviewed grant from the Canadian Institutes of Health Research (201503) and is registered on Clinicaltrials.gov NCT02650791. It has been approved by the Ottawa Health Science Network Research Ethics Board. Study results will presented at national and international conferences. Importantly, the results of this trial will inform the feasibility and conduct of a larger study.

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Strengths and limitations of this study

- Pilot randomized study (Vanguard design) to better assure feasibility and inform the design of a larger randomized study in recipients of autologous hematopoietic stem cell transplantation.
- First study in autologous hematopoietic stem cell transplantation to evaluate a strategy of prophylactic tranexamic acid with prophylactic platelet transfusions to prevent bleeding.
- First prospective study to concurrently utilize 2 bleeding scales – WHO and BSMS bleeding scales to better appreciate clinically relevant bleeding.
- The trial will collect health related quality of life data using a variety of validated scales within the context of bleeding risk and autologous hematopoietic stem cell transplantation.
- A limitation of this study is the absence of a "third" control arm, where participants only receive therapeutic platelets (without prophylactic platelets or prophylactic tranexamic acid.

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INTRODUCTION

1.1 Background and rationale

1.1.1 What is the problem to be addressed?

In Canada, over 1,500 autologous hematopoietic stem cell transplantations (ASCT) are performed annually for hematologic malignancies.[1] It is currently standard practice to provide a prophylactic transfusion of platelets to prevent bleeding when the daily measured platelet count is less than 10 x 10^9/L.[2-5] A patient may require up to six adult platelet doses during the post-transplant period.[6] However, the true benefit of prophylactic platelet transfusions in the ASCT setting is unclear and has been called into question by several recent studies.[7-9] Prophylactic platelet transfusions may not only be unnecessary, they may be detrimental to the patient. Among blood products, platelet transfusions are associated with the highest risk of both infectious and non-infectious complications: this would include bacterial infections and allergic /febrile reactions (Table 1).[10-13]

Table 1: Platelet Transfusion Risks*

Risk of Event	Event
1 in 20	Febrile non-hemolytic transfusion reaction per pool of platelets
1 in 100	Minor allergic reactions (urticaria)
1 in 300	Febrile non-hemolytic transfusion reaction per unit of RBC (1 'donor exposure')
1 in 700	Transfusion-associated circulatory overload per transfusion episode
1 in 7,000	Delayed hemolytic transfusion reaction
1 in 10,000	Transfusion-related acute lung injury (TRALI)
1 in 10,000	Symptomatic bacterial sepsis per pool of platelets
1 in 40,000	ABO-incompatible transfusion per RBC transfusion episode
1 in 40,000	Serious allergic reaction per unit of component
1 in 60,000	Death from bacterial sepsis per pool of platelets
1 in 153,000	Death from bacterial sepsis per pool of platelets
1 in 250,000	Symptomatic bacterial sepsis per unit of RBC
1 in 500,000	Death from bacterial sepsis per unit of RBC
<1 in 1,000,000	Transmission of West Nile Virus
1 in 2,300,000	Transmission of hepatitis C virus per unit of component
1 in 4,000,000	Transmission of Chagas disease per unit of component
1 in 4,300,000	Transmission of HTLV per unit of component
1 in 7,800,000	Transmission of human immunodeficiency virus (HIV) per unit of component

*http://ibta.ir/en/wp-content/uploads/111_Bloody-Easy_3rd-1.pdf

Moreover, the potential overuse of platelet products places a significant burden on a scarce health care resource that is provided through volunteer donations. This concern is further highlighted by the 2 recent "alert" warnings of significant platelet shortages or potential

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shortages either regionally or nationally issued by the Canadian Blood Services [personal communication, R. Trifulnov, Canadian Blood Services 2015].

An alternative strategy to prevent bleeding and reduce the need for platelet transfusions involves administering Tranexamic Acid, an oral antifibrinolytic agent to stabilize blood clots and reduce bleeding.[14] Tranexamic Acid is safe and effective in many clinical scenarios,[15 16] and may be a reasonable alternative for prophylactic platelet transfusions. In the setting of ASCT, Tranexamic Acid may reduce bleeding and further enhance a strategy of therapeutic platelet transfusions where platelets are administered only in the event of active bleeding symptoms.

The effect of prophylactic platelet transfusions and Tranexamic Acid on clinical, quality of life and economic outcomes in patients receiving ASCT is unknown. Our overarching goal is to perform a randomized controlled trial to determine whether a strategy of prophylactic Tranexamic Acid (with therapeutic platelet transfusions) is safe and effective compared to prophylactic platelet transfusions in patients undergoing ASCT. Before conducting a larger trial, we first propose a pilot randomized controlled trial to determine the feasibility of such a study.

1.1.2 Why is a trial needed now?

The evidence supporting the use of prophylactic platelets to prevent bleeding in ASCT is weak and platelets remain the scarcest blood resource with the highest complication rate of all blood products. Patients undergoing transplant represent an important proportion of patients receiving platelet transfusions and there is a need to identify an alternative strategy to prevent and control bleeding in this high risk population. Clinical trials evaluating the effectiveness of platelet transfusions in malignant hematology patients are heterogeneous and have included patients being treated with a variety of modalities, including high-dose chemotherapy, autologous and allogeneic transplantation. They have examined different prophylactic platelet transfusion thresholds, different platelet doses, and a solely therapeutic platelet transfusion strategy (i.e. no Tranexamic Acid or other antifibrinolytic agent). In the latter circumstance, a therapeutic platelet transfusion strategy did not appear to increase bleeding in subgroup analyses of patients undergoing ASCT.[7 9] A strategy of prophylactic Tranexamic Acid combined with therapeutic platelet transfusions may reduce bleeding, platelet transfusions and the adverse consequences associated with platelet transfusions.

1.1.3 Platelet Transfusion Requirements in Autologous Stem Cell Transplantation

In Canada, over 1,500 ASCT are performed annually.[1] A patient undergoing ASCT typically receives 1-6 adult platelet doses in the post-transplant period.[9 17-21] All adult transplant centres in Canada routinely prescribe prophylactic platelet transfusions when the daily measured platelet count is less than 10 x 10^9/L.[22] Indeed, this is the practice at our centre, where an average of 6 adult platelet doses are transfused in the first 60 days following transplant.[6]

1.1.4 Are Prophylactic Platelet Transfusions Beneficial?

The practice of prophylactic platelet transfusions began following the publication of an observational study in acute leukemia patients in the early 1960s that observed an increase in the

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number of days with bleeding with worsening thrombocytopenia.[23] However, the onset of major bleeding was not clearly related to a specific platelet threshold. Moreover, a review of 3000 thrombocytopenic adult oncology patients over a 10-year period, did not demonstrate a correlation between platelet count and the risk of haemorrhage.[24] Patient-specific factors, including recent bleeding and recipients of hematopoietic stem cell transplantation, rather than platelet counts were associated with increased risk and severity of bleeding. Counter-intuitively, a study of platelet count recovery following hematopoietic stem cell transplantation reported that most clinically important bleeding events occurred when the morning platelet count was greater than 20 x 10^9/L.[25] Finally, a review of all case reports of severe intracranial hemorrhage from studies of prophylactic platelet transfusions found no association between the occurrence of major (intracranial) bleeding and the platelet count just prior to bleeding.[26]

1.1.5 Therapeutic Versus Prophylactic Platelet Transfusion Strategies: Randomized Controlled Trials

Despite the fact that administering prophylactic platelet transfusions to patients with severe thrombocytopenia is a common practice, in several clinical settings this practice is poorly supported by evidence. The best evidence for a prophylactic platelet strategy is in acute leukemia patients.[7] It has been proposed that patients undergoing ASCT and those with chronic, stable thrombocytopenia[9 27] may be effectively managed with a therapeutic transfusion strategy, thus minimizing the need for unnecessary transfusions and their associated risks.

Until recently, the only evidence to support a prophylactic platelet transfusion strategy rather than a therapeutic strategy resulted from three small randomized trials in patients undergoing high dose therapy for acute leukemia in the 1970s.[28-30] In two studies, bleeding events were lower in the patients receiving prophylactic platelet transfusions[28 29] and in two studies, platelet transfusions were reported to be decreased in the patients receiving therapeutic transfusions.[29 30] However, it was difficult to draw any definitive conclusions from these studies as they are older, included small numbers of patients who received aspirin therapy as an anti-pyretic and suffered from various methodological limitations.

More recently, two large randomized controlled trials comparing prophylactic and therapeutic platelet transfusion strategies in patients with hematologic malignancies have been published. Firstly, Wandt and colleagues randomized 396 patients undergoing chemotherapy for acute myeloid leukemia or ASCT, to either prophylactic versus therapeutic platelet transfusions. Grade 2 (moderate bleeding not requiring transfusion) or greater bleeding using a modified World Health Organization (WHO) scale occurred in 65 (19%) patients in the prophylactic group and 127 (42%) patients in the therapeutic group ($p<0.0001$).[9] Additionally, there was increase in grade 4 bleeding – 13(7%) versus 4(2%), $p=0.0095$, in patients with acute leukemia in the therapeutic arm. In contrast, in patients undergoing ASCT there was no difference in incidence of grade 3 bleeding or grade 4 bleeding events were observed in either arm. The mean number of platelet transfusions was reduced by 33.5%, ($p<0.0001$) in the therapeutic arm. The authors concluded that prophylactic platelet transfusions should remain the standard of care for patients undergoing treatment for acute leukemia, but a therapeutic strategy could be possibly adopted for patients undergoing ASCT.

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Similarly, the TOPPS investigators[7] randomized patients with a variety of hematologic malignancies undergoing chemotherapy, autologous or allogeneic stem cell transplantation to either a prophylactic or therapeutic platelet transfusion strategy. The primary end point, WHO grade 2 bleeding or greater, occurred in 151 (50%) patients in the therapeutic group and 128 (43%) patients in the prophylactic group, (p=0.06 for non-inferiority). In a predefined subgroup analysis of patients undergoing ASCT, there was no difference in grade 2 bleeding or higher between the groups – 99/210 (47%) patients in the therapeutic group versus 95/210 (45%) patients in the prophylactic group. For the entire study population, fewer patients in the therapeutic group received platelet transfusions – 176 (59%) versus 266 (89%), p<0.001. The authors concluded that prophylactic platelet transfusions should remain the standard of care, but identified that a therapeutic strategy in the ASCT setting warrants further investigation. It is notable that neither the Wandt et al. nor the TOPPS trial were adequately powered to evaluate bleeding risk in the ASCT setting.

1.1.6 Are Platelet Transfusions Harmful?

Among blood products, platelets are associated with the highest risk of transfusion-related infectious and non-infectious complications.[10-13] Some complications associated with platelet transfusions include fevers, rigors, acute lung injury, volume overload, hemolysis, platelet refractoriness, bacterial contamination, and rarely, viral transmission. Though some of these reactions are mild, they often require discontinuation of the transfusion and another transfusion at a later time. This adds stress to the limited platelet inventory, and can also increase patient length of stay, and increase patient anxiety. There is also an emerging body of literature that suggests that transfusions may modulate immunologic function and adversely affect treatment outcome in hematologic malignancies. In a study of acute leukemia patients, increased platelet transfusions during induction was associated with decreased survival[31] and we have recently demonstrated an association between transplant-related morbidity and mortality with the number of platelet transfusions.[6]

1.1.7 Therapeutic Versus Prophylactic Platelet Transfusion Strategies In Patients Undergoing Autologous Hematopoietic Stem Cell Transplantation

As described above, the results of two recent randomized controlled trials lead us to question the value of prophylactic platelet transfusions in patients undergoing ASCT. Additional evidence for the efficacy of a therapeutic platelet transfusion strategy in this patient group was reported by Wandt et al.[8] They instituted a therapeutic platelet transfusion strategy in consecutive, clinically stable patients undergoing ASCT. Bleeding events were observed in only 26 of the 140 (19%) transplants. The maximum severity was WHO grade 2, with no grade 3 or 4 bleeding. Notably, 47% of high-dose melphalan transplants for multiple myeloma (the most common indication for ASCT) were performed without any platelet transfusions and platelet use was decreased by 53%.

Despite the results of these studies, the Canadian ASCT community remains reluctant to embrace and adopt the use of therapeutic platelet strategy in the ASCT setting. At the same, there is an increasing concern that prophylactic platelet transfusions may not be warranted in all patients.

1.1.8 Tranexamic Acid: An Alternative Prophylactic Strategy

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Tranexamic Acid, an antifibrinolytic agent, is a synthetic analog of the amino acid lysine and competitively inhibits the activation of plasminogen to plasmin, thereby reducing the degradation of fibrin, a protein that forms the framework of blood clots. It has been extensively studied in surgical settings where it has been shown to consistently reduce bleeding and transfusion needs.[32-37] Further, it is commonly and safely employed (Table 2) in the management of patients with bleeding disorders such as hemophilia and von Willebrand Disease.[38 39]

Table 2: Tranexamic Acid Risks*

Adverse Reactions Significant

>10%:

1. Central nervous system: Headache (50%)
2. Gastrointestinal: Abdominal pain (20%)
3. Neuromuscular & skeletal: Back pain (21%), muscle pain (11%)
4. Respiratory: Nasal/sinus symptoms (25%)

1% to 10%:

1. Central nervous system: Fatigue (5%)
2. Hematologic: Anemia (6%)
3. Neuromuscular & skeletal: Arthralgia (7%), muscle cramps/spasms (7%)

All formulations: <1% (Limited to important or life-threatening): Allergic skin reaction, anaphylactic shock, anaphylactoid reactions, cerebral thrombosis, deep vein thrombosis (DVT), diarrhea, dizziness, nausea, pulmonary embolism, renal cortical necrosis, retinal artery/vein obstruction, seizure, ureteral obstruction, visual disturbances (including impaired color vision and loss), vomiting

*http://www.uptodate.com/contents/tranexamic-acid-drug-information?source=preview&search=%2Fcontents%2Fsearch&anchor=F229896&selectedTitle=1~78#F229896

As some patient groups (e.g. those undergoing induction therapy for acute leukemia) appear to be at higher risk for clinically relevant bleeding, efforts are shifting to try and identify strategies to reduce the risk of bleeding while minimizing patient exposure to blood products. Consequently, there has been interest in its prophylactic use in patients with hematologic malignancies in the context of hypoproliferative thrombocytopenia to prevent bleeding.[15 16]

Taken together, a strategy using prophylactic Tranexamic Acid with therapeutic platelet transfusions can be considered a potential substitute for a strategy of prophylactic platelet transfusions in patients at risk for bleeding.

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1.1.9 Assessment of bleeding and quality of life associated with thrombocytopenia in patients undergoing Autologous Hematopoietic Stem Cell Transplantation

Bleeding has been the primary outcome of all the large randomized controlled trials assessing platelet transfusions in patients with hematologic malignancies.[2 4] Almost all these trials have used bleeding scores based on the World Health Organization bleeding score, which classifies bleeding into 4 grades: 1 – mild; 2 – moderate bleeding not requiring red cell transfusions; 3 – moderate to severe bleeding requiring red blood cell transfusion; 4 – life or limb- threatening bleeding.[40] However, the WHO bleeding score has definite limitations including the lack of precise definitions for each bleeding grade and the lack of formal validation.[41 42] Grade 2 bleeding or greater bleeding has been used as the primary outcome in most clinical trials, primarily due to rarity of grade 3 and 4 bleeding. The lack of standardization of bleeding when using the WHO bleeding score has resulted in variation in the type and amount of bleeding reported in clinical trials.[43] Additionally, the validity of grade 2 bleeding as the primary outcome measure is problematic as grade 2 bleeding does not predict more severe grade 3 or 4 bleeding, and has never been shown to predict mortality or major morbidity, or be associated with changes in Quality of Life outcomes.[41 44] To address some of these shortcomings in the assessment of bleeding, Webert et al. used measurement theory to develop a validated and reliable bleeding score in patients with hematological malignancies.[45] Outcomes beyond bleeding also need to be considered in clinical trials evaluating platelet transfusions or alternative strategies to prevent bleeding in patients with hematologic malignancies.

Although the rarity of mortality directly related to bleeding precludes its use as a primary outcome in platelet transfusion studies, Quality of Life is an important outcome that assesses the impact of morbidity related both to bleeding and adverse outcomes related to transfusions or medications.[46 47] Ideally, this would be done using both general Quality of Life scales such as the EQ-5D[48] and disease specific scales for thrombocytopenia such as the FACT – thrombocytopenia 18. [49]

1.1.10 Patient and Caregiver Engagement in Clinical Trial Design

Patient and/or informal caregiver's perspective(s) are rarely considered in clinical trials where health care professionals independently determine clinical endpoints. For instance, what degree of bleeding is important from patient's perspective? Are there psychosocial or anxiety concerns that relate to thrombocytopenia? Which endpoint(s) are most pertinent from the patient's perspective? As championed by the Patient-Centered Outcomes Research Institute (PCORI)[50], there has been increasing interest and efforts to engage patients and caregivers to design clinical trials that are relevant and meaningful to the patient. To our knowledge, this has never been studied within the context of bleeding prevention strategies in patients receiving ASCT.

1.1.11 Summary: The Importance of the Problem

It is routine clinical practice to administer prophylactic platelets to prevent bleeding in patients undergoing ASCT. However, the true benefit of prophylactic transfusion to prevent bleeding is unknown. Sub-group analyses from of three recent studies suggest that this population is at low risk for clinically relevant bleeding[7-9] and that the number of platelet transfusions can be

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significantly reduced by adopting a therapeutic transfusion strategy. This approach has not been accepted in practice due to ongoing concerns of bleeding risk.

Platelet transfusions are not benign. Inherent risks include fever, rigors, hemolysis, acute lung injury, transfusion associated circulatory overload, bacterial and rarely, viral, transmission.10-13 The routine use of frequent platelet transfusions may also increase the risk for alloimmune refractoriness, which may increase the difficulty in treating or preventing bleeding complications. The immune-modulatory effect of platelets may result increase post-transplant toxicity and increase the risk of tumour progression.[6,26] Platelets, in particular single-donor platelets are often in short supply due to reliance on volunteer donation with a shelf-life of only 5 days.[46] Finally, the impact of prophylactic platelet transfusions on the patient's quality of life is largely unknown.

In patients undergoing ASCT, an alternative approach to prophylactic platelet transfusions to prevent bleeding is to administer prophylactic Tranexamic Acid. Tranexamic Acid is safe, extensively used to prevent bleeding and reduces red cell transfusions in many clinical settings. In contrast to a solely therapeutic platelet transfusion strategy, this cautious approach has the potential to both minimize platelet use and provide this vulnerable population with a safe and effective prophylactic strategy.

In summary, there is a need to reduce the use of unnecessary platelet transfusions and Tranexamic Acid represents a transfusion-free alternative to prevent bleeding in recipients of ASCT.

1.2 Objectives and Hypothesis

We hypothesize that in patients undergoing autologous hematopoietic stem cell transplantation (ASCT), a strategy of prophylactic Tranexamic Acid with therapeutic platelet transfusions for bleeding 1) is safe, 2) improves quality of life, and 3) improves economic outcomes as compared to prophylactic platelet transfusions.

1.3 Trial Overview and Design

PATH is an open-labeled multi-center pilot feasibility parallel-arm 1:1 randomized controlled trial, where participants will be stratified by centre and disease (either myeloma or other hematologic malignancy). We will recruit patients over a 2 year period and follow each participant for a minimum of 30 days.

PATH has been funded by a peer reviewed grant by Canadian Institutes of Health Transitional Open Grant 2014-2015 (RN260949 - 342593) and is registered on the National Institute of Health, Clinicaltrials.gov registry (NCT02650791).

METHODS AND ANALYSIS

Methods and Analysis: Participants, Interventions and Outcomes

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2.1 *Study Setting*

PATH will be carried out at 3-4 tertiary Adult Hematopoietic Stem cell transplant centres in Canada.

2.2 Eligibility criteria

Recipients of ASCT should be screened for study eligibility prior to initiation of conditioning chemotherapy and /or radiotherapy. Screening should occur, ideally in a dedicated outpatient clinic prior to hospital admission for ASCT. Inclusion and Exclusion criteria must be satisfied prior to randomization as outlined in Section 2.2.1 and 2.2.2. Randomization will be performed on day 0 of the ASCT. Verification that patients still meet all inclusion and exclusion criteria will occur prior to patients being randomized.

2.2.1 Inclusion Criteria

1. Adults 18 years or older undergoing ASCT for a hematologic malignancy
2. Patients providing written informed consent prior to starting transplantation

2.2.2 Exclusion Criteria

1. A previous WHO grade 3 or 4 bleeding event
2. A WHO grade 2 bleeding event within the past year
3. A previous or current thrombotic event defined as a pulmonary embolism, deep vein thrombosis, cerebral thrombosis
4. Active angina (chest pain of presumed cardiac origin either at rest or with activity)
5. Current or previous (within 2 weeks) urinary tract bleeding
6. An inherited hemostatic or thrombotic disorder
7. Coagulopathy defined as a prothrombin time or activated partial thromboplastin time more than 1.5 times the upper limit of normal or fibrinogen less than 2 g/L
8. A requirement for anticoagulant or antiplatelet drugs
9. Previously documented history of refractoriness to platelet transfusion secondary to HLA antibodies
10. Significant renal impairment (creatinine more than 1.5 times the upper limit of normal)
11. Pregnant or breast-feeding
12. Unwilling or unable to provide informed consent
13. Participant has known history of subarachnoid hemorrhage
14. Participant has acquired disturbances to his/her colour vision
15. Participant has known sensitivity or allergy to Tranexamic Acid or any of its ingredients
16. The current use of Oral Contraceptive Pill (Birth Control Pill), Hormonal Contraceptives or Hormone Replacement Therapy.

The use of any other concomitant medications would be at the discretion of the treating physician and his/her team.

2.3 Interventions

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All patients undergoing ASCT have daily morning laboratory investigations, including a complete blood count (CBC), performed as part of standard care. We will randomize patients to one of the following bleeding prevention strategies from the day of stem cell infusion (day 0) until platelet engraftment (defined as the first of two consecutive measured platelet counts on different days that are greater than 20 x 10^9/L and increasing in the absence of a platelet transfusion for three consecutive days), or day 30 post ASCT, whichever comes first):

2.3.1 Control Arm: Prophylactic Platelet Transfusion Strategy

Patients allocated to the prophylactic platelet transfusion group will receive a platelet transfusion when the measured platelet count is less than 10 x 10^9/L.

2.3.2 Experimental Arm: Prophylactic Tranexamic Acid Strategy

Patients allocated to the prophylactic Tranexamic Acid group will receive a standardized routine oral dose of Tranexamic Acid 1 gram three times daily. Tranexamic Acid will start when Platelet count is less than 50 x 10^9/L and continue until platelet engraftment. Patients in this group will not receive routine prophylactic platelet transfusions.

This is not a blinded study. All patients will have their platelet count checked daily or per institutional policy until platelet engraftment. *All patients in both study arms will receive therapeutic platelet transfusions to treat clinically relevant bleeding, defined as World Health Organization (WHO) bleeding of grade 2 or greater.* The WHO grading system is the most commonly used tool in the assessment of bleeding events in platelet transfusion trials.[43] In this system, bleeding episodes are categorized as grade 1 (mild), grade 2 (moderate; red cell transfusion no needed immediately), grade 3 (severe; requiring red cell transfusion within 24 hours), and grade 4 (debilitating or life-threatening; see Table 3).[40] Further, we will also assess bleeding using the Bleeding Severity Measurement Scale.[45]

Table 3: World Health Organization Bleeding Grades

Score	*Bleeding Symptoms*
0	None
1	Petechiae, ecchymosis, occult blood in body secretions, mild vaginal spotting, epistaxis lasting less than 30 minutes
2	Evidence of gross hemorrhage not requiring red cell transfusion over routine transfusion needs: epistaxis lasting greater than or equal to 30 minutes, hematuria, hematemesis, hematoma, hematochezia
3	Hemorrhage requiring transfusion of one or more units of red cells within 24 hours
4	Life-threatening hemorrhage, defined as either massive bleeding causing hemodynamic compromise or bleeding into a vital organ (e.g., intracranial, pericardial, or pulmonary hemorrhage) or death.

2.3.3 Therapeutic Platelet Transfusions

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All patients may receive therapeutic platelet transfusions for grade 2 bleeding or greater regardless of the platelet count. Therapeutic platelet transfusions can also be given to patients who become clinically unstable, defined as the presence of fever, active infection, or hypotension, and those who require an invasive procedure. Therapeutic platelet transfusions may be administered at any time at the clinician's discretion and the rationale will be recorded. The type of platelet product will follow local institutional practices.

2.3.4 Source of Progenitor cells, Conditioning Regimen and Supportive Care

For all patients, the choice of progenitor cells and conditioning regimen will be determined by the centre and by availability. Similarly, the supportive care strategy will be determined by local institutional policy. This will include, but not limited to the use of antibiotics, analgesia, IV fluids, growth factors and other blood products (not including platelets).

2.4 Outcomes

2.4.1 Primary Outcome (Feasibility)

The primary outcomes of this feasibility trial will be:

1. Enrolment,
2. Number of off-protocol platelet transfusions, and
3. Total number of platelet transfusion per group.
4. Adherence to Tranexamic Acid use

We will evaluate feasibility by:

1. Recruitment of an average of 2 patients per month per site,
2. Fewer than 10% off-protocol transfusions in each arm, and
3. An absolute reduction of 25% in the total number of platelet transfusions in the Tranexamic Acid arm.
4. Adherence to Tranexamic Acid use. Adherence to Tranexamic Acid use will be defined as follows: Excellent (≥90% consumed), Acceptable (between 75% and 90% consumed), Poor (≤75% consumed). We anticipate Acceptable to Excellent adherence given that study participants will be cared for in an inpatient setting.

During the feasibility trial we will identify any logistical issues related to protocol implementation, randomization strategy or data collection. Furthermore, we will define the sample size required for the definitive trial.

2.4.2 Secondary Outcomes (Clinical)

The secondary outcomes of this trial will be:

1. WHO bleeding events of grade 2 or higher[40]
2. WHO bleeding events of grade 3 or 4[40]
3. Time from randomization to bleeding of WHO grade 2 or higher[40]
4. Number of days with bleeding of WHO grade 2 or higher

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5. Bleeding Severity Measurement Scale (BSMS; Table 4)[45] bleeding events of grade 2.
   - Previous studies have used the WHO bleeding scale and have reported substantial inter-observer variability in scoring.[51] Hence, we have elected to use a validated score that has been shown to minimize this variability, in addition to the WHO scale in order to facilitate comparison with other large clinical trials

Table 4: Bleeding Severity Measurement Scale (BSMS)

Bleeding grade and classification		**Description of bleeding**
0. No Bleeding		No bleeding.
1. Not clinically significant bleeding	1(a) Trace bleeding	Minimal bleeding or bleeding detectable by laboratory measures only. Bleeding does not have any impact on patient or on the level of care provided to the patient.
	1(b) Mild bleeding	Non–clinically significant bleeding. Bleeding does not have any impact on patient or level of care provided to the patient.
2. Clinically significant bleeding	2(a) Serious bleeding	Bleeding directly resulting in one or more of the following: · Significant pain (requiring medical treatment or intervention) · Need for interventions (including transfusion, surgery, invasive procedures, administration of medication, etc.)
	2(b) Serious bleeding causing significant morbidity	Any bleeding meeting one or more of the following criteria: · All central nervous system bleeding · Resulting in hemodynamic instability: -Tachycardia (increase in resting heart rate by at least 20 bpm) or -Hypotension (decrease in systolic and/or diastolic BP by at least 20 mmHg) · Resulting in vision loss · Resulting in significant morbidity
	2(c) Fatal bleeding	Any bleeding directly contributing to patient's death

6. Number of platelet transfusions
7. Number of red cell transfusions:
8. Time to platelet count recovery
9. Number of days with platelet count < 10 x 10^9/L
10. Length of hospital stay:
11. Number and type of adverse transfusion reactions
12. Bearman toxicity score (Table 5)[52]:

Table 5: Bearman Toxicity Grading Scale

Toxicity	***Grade 1***	***Grade 2***	***Grade 3***
Heart	Mild electrocardiogram abnormality, not requiring medical intervention; or noted heart enlargement on CXR with no clinical symptoms	Moderate electrocardiogram abnormalities requiring and responding to medical intervention; or requiring continuous monitoring without treatment; or congestive heart failure responsive to digitalis or	Severe electrocardiogram abnormalities with no or only partial response to medical intervention; or heart failure with no or only minor response to medical intervention: or decrease in voltage by more than 50%

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Toxicity	Grade 1	Grade 2	Grade 3
		diuretics	
Bladder	Macroscopic hematuria after 2 days from last chemotherapy dose with no subjective symptoms of cystitis and not caused by infection	Macroscopic hematuria after 7 days from last chemotherapy dose not caused by infection; or hematuria after 2 days with subjective symptoms of cystitis not caused by infection	Hemorrhagic cystitis with frank blood, necessitating invasive local intervention with installation of sclerosing agents, nephrostomy or other surgical procedures
Kidney	Increase in creatinine up to twice the baseline value	Increase in creatinine above twice baseline but not requiring dialysis	Requirement of dialysis
Lung	Dyspnea without CXR changes not caused by infection or congestive heart failure; or CXR showing isolated infiltrate or mild interstitial changes without symptoms not caused by infection or congestive heart failure	CXR with extensive localized infiltrate or moderate interstitial changes combined with dyspnea and not caused by infection or CHF; or decrease of PO_2 (>10% from baseline) but not requiring mechanical ventilation or >50% O_2 on mask and not caused by infection	Interstitial changes requiring mechanical ventilatory support or >50% oxygen on mask and not caused by infection or CHF
Liver	Mild hepatic dysfunction with 2.0 mg/dl <bilirubin <6.0 mg/dl or weight gain >2.5% and <5% from baseline, of noncardiac origin; or serum AST increase more than two-fold but less than five-fold from lowest preconditioning	Moderate hepatic dysfunction with bilirubin >6 mg/dl <20 mg/dl; or serum AST increase >five-fold from preconditioning; or clinical ascites or image-documented ascites >100 ml; or weight gain >5% from baseline of noncardiac origin	Severe hepatic dysfunction with bilirubin >20 mg/dl; or hepatic encephalopathy; or ascites compromising respiratory function
CNS	Somnolence but the patient is easily arousable and oriented after arousal	Somnolence with confusion after arousal; or other new objective CNS symptoms with no loss of consciousness not more easily explained by other medication, bleeding, or CNS infection	Seizures or coma not explained (documented) by other medication, CNS infection, or bleeding
Stomatitis	Pain and/or ulceration not requiring a continuous i.v. narcotic drug	Pain and/or ulceration requiring a continuous i.v. narcotic drug (morphine drip)	Severe ulceration and/or mucositis requiring preventive intubation; or resulting in documented aspiration pneumonia with or without intubation
GI toxicity	Watery stools >500 ml but <2000 ml every day	Watery stools >2000 ml every day not related to	Ileus requiring nasogastric suction

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Toxicity	Grade 1	Grade 2	Grade 3
	not related to infection	infection; or macroscopic hemorrhagic stools with no effect on cardiovascular status not caused by infection; or subileus not related to infection	and/or surgery and not related to infection; or hemorrhagic enterocolitis affecting cardiovascular status and requiring transfusion

13. Incidence of infections at Day 30 following ASCT:
    - Clinically important infections will be ascertained using Centre for Disease Control criteria where grade 4 and 5 infections will be recorded
14. Mortality at Day 30
15. Quality of Life measures: FACT-Thrombocytopenia 18 (Table 6)[49], FACT-BMT (Table 7)[53], GAD-7 (Table 8)[54] and EQ-5D (Table 9)[48]

Table 6: FACT-Thrombocytopenia-18

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4

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GS3	I get support from my friends.....	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4
GS5	I am satisfied with family communication about my illness.....	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support).....	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please m☐k this box and go to the*					
GS7	I am satisfied with my sex life	0	1	2	3	4

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

	<u>EMOTIONAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	<u>FUNCTIONAL WELL-BEING</u>	**Not at all**	**A little bit**	**Some -what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling.....	0	1	2	3	4

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GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4
GF7	I am content with the quality of my life right now	0	1	2	3	4

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

	ADDITIONAL CONCERNS	**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

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Th 12	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 15	For women only: I am bothered by vaginal bleeding	0	1	2	3	4

Table 7: FACT-BMT

Below is a list of statements that other people with your illness have said are important. **Please circle or mark one number per line to indicate your response as it applies to the past 7 days.**

	PHYSICAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GP1	I have a lack of energy	0	1	2	3	4
GP2	I have nausea	0	1	2	3	4
GP3	Because of my physical condition, I have trouble meeting the needs of my family	0	1	2	3	4
GP4	I have pain	0	1	2	3	4
GP5	I am bothered by side effects of treatment	0	1	2	3	4
GP6	I feel ill	0	1	2	3	4
GP7	I am forced to spend time in bed	0	1	2	3	4

	SOCIAL/FAMILY WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GS1	I feel close to my friends	0	1	2	3	4
GS2	I get emotional support from my family	0	1	2	3	4
GS3	I get support from my friends	0	1	2	3	4
GS4	My family has accepted my illness	0	1	2	3	4

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GS5	I am satisfied with family communication about my illness	0	1	2	3	4
GS6	I feel close to my partner (or the person who is my main support)	0	1	2	3	4
Q1	*Regardless of your current level of sexual activity, please answer the following question. If you prefer not to answer it, please mark this box* ☐ *and go to the next section.*					
GS7	I am satisfied with my sex life	0	1	2	3	4

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

	EMOTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GE1	I feel sad	0	1	2	3	4
GE2	I am satisfied with how I am coping with my illness	0	1	2	3	4
GE3	I am losing hope in the fight against my illness	0	1	2	3	4
GE4	I feel nervous	0	1	2	3	4
GE5	I worry about dying	0	1	2	3	4
GE6	I worry that my condition will get worse	0	1	2	3	4

	FUNCTIONAL WELL-BEING	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
GF1	I am able to work (include work at home)	0	1	2	3	4
GF2	My work (include work at home) is fulfilling	0	1	2	3	4
GF3	I am able to enjoy life	0	1	2	3	4
GF4	I have accepted my illness	0	1	2	3	4
GF5	I am sleeping well	0	1	2	3	4
GF6	I am enjoying the things I usually do for fun	0	1	2	3	4

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GF7	I am content with the quality of my life right now.....	0	1	2	3	4

	ADDITIONAL CONCERNS	**Not at all**	**A little bit**	**Some-what**	**Quite a bit**	**Very much**
BMT1	I am concerned about keeping my job (include work at home).....	0	1	2	3	4
BMT2	I feel distant from other people	0	1	2	3	4
BMT3	I worry that the transplant will not work.....	0	1	2	3	4
BMT4	The side effects of treatment are worse than I had imagined	0	1	2	3	4
C6	I have a good appetite.....	0	1	2	3	4
C7	I like the appearance of my body	0	1	2	3	4
BMT5	I am able to get around by myself	0	1	2	3	4
BMT6	I get tired easily	0	1	2	3	4
BL4	I am interested in sex.....	0	1	2	3	4
BMT7	I have concerns about my ability to have children	0	1	2	3	4
BMT8	I have confidence in my nurse(s).....	0	1	2	3	4
BMT9	I regret having the bone marrow transplant.....	0	1	2	3	4
BMT10	I can remember things	0	1	2	3	4
Br1	I am able to concentrate.....	0	1	2	3	4
BMT11	I have frequent colds/infections.....	0	1	2	3	4
BMT12	My eyesight is blurry.....	0	1	2	3	4
BMT13	I am bothered by a change in the way food tastes.....	0	1	2	3	4
BMT14	I have tremors	0	1	2	3	4
B1	I have been short of breath	0	1	2	3	4
BMT15	I am bothered by skin problems (e.g., rash, itching)	0	1	2	3	4

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BMT16	I have trouble with my bowels	0	1	2	3	4
BMT17	My illness is a personal hardship for my close family members	0	1	2	3	4
BMT18	The cost of my treatment is a burden on me or my family.....	0	1	2	3	4

Table 8: GAD-7

Over the last 2 weeks, how often have you been bothered by any of the following problems?	Not at all	Several days	More than half the days	Nearly every day
Feeling nervous, anxious or on edge	0	1	2	3
Not being able to stop or control worrying	0	1	2	3
Worrying too much about different things	0	1	2	3
Trouble relaxing	0	1	2	3
Being so restless that it is hard to sit still	0	1	2	3
Becoming easily annoyed or irritable	0	1	2	3
Feeling afraid as if something awful might happen	0	1	2	3

Table 9: EQ-5D

By placing a tick in one box in each group below, please indicate which statements best describe your own health state today.

Mobility

I have no problems in walking about ❑

I have some problems in walking about ❑

I am confined to bed ❑

Self-Care

I have no problems with self-care ❑

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I have some problems washing or dressing myself ❑
I am unable to wash or dress myself ❑

Usual Activities (*e.g. work, study, housework, family or leisure activities)*
I have no problems with performing my usual activities ❑
I have some problems with performing my usual activities ❑
I am unable to perform my usual activities ❑

Pain/Discomfort
I have no pain or discomfort ❑
I have moderate pain or discomfort ❑
I have extreme pain or discomfort ❑

Anxiety/Depression
I am not anxious or depressed ❑
I am moderately anxious or depressed ❑
I am extremely anxious or depressed ❑

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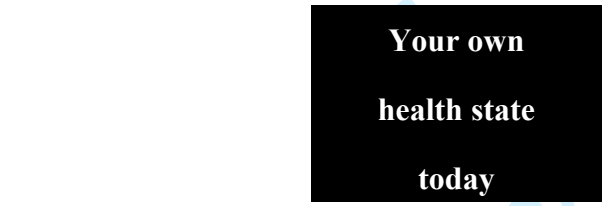
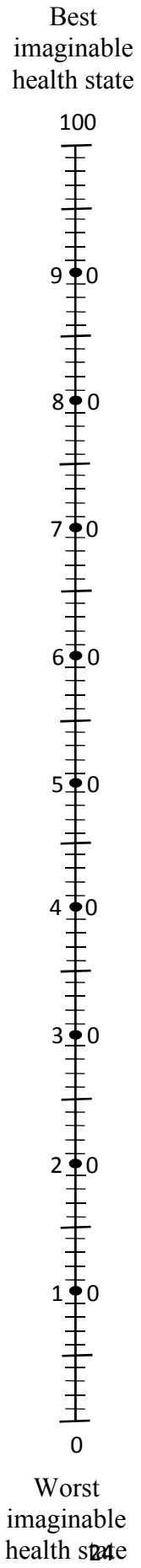
We would like you to indicate on this scale how good or bad your own health is today, in your opinion. Please do this by drawing a line from the box below to whichever point on the scale indicates how good or bad your health state is today.





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16. Economic Analyses: incremental cost effectiveness ratios

2.5 Participant timeline

All patients will be followed for 30 days post ASCT. The assigned treatment protocol will be applied from Day 0 of ASCT to platelet engraftment or Day 30, whichever comes first. Assessments of clinical outcomes will occur as detailed in Table 10 until Day30.

Table 10: Schedule of Activities

Type of visit	**Screening**	**Enrollment**	**Randomization**	**Week 1**	**Week 2**	**Week 3**	**Week 4**
Screening							
Timing of visit		Pre-ASCT*	Day 0				
Confirm eligibility criteria	x	x	x				
Informed Consent	x						
Baseline Characteristics							
Demographic data		x					
Disease, treatment history		x					
ECOG and Karnofsky performance status		x					
Comorbidities		x					
Bleeding history		x					
Bleeding assessment (WHO & BSMS)		x					
Interventions^							
Daily Oral Tranxaemic Acid† or Prophylactic Platelets~				x	x	x	x
Assessments							
Complete Blood Count‡			x	x	x	x	x
Daily bleeding assessments (WHO & BSMS)^			x	x	x	x	x
Bearman Toxicity Scale							x
Daily NCI Toxicity Criteria Assessment for SAEs and AEs				x	x	x	x
Quality of Life Assessments#							
FACT-BMT		x		x	x	x	x
FACT-Thrombocytopenia 18		x		x	x	x	x
EQ-5D		x		x	x	x	x
GAD-7		x		x	x	x	x

** The enrollement visit should occur within 14 days prior to start of conditioning chemotherapy*

‡ Daily or as per institutional policy

^ From Day 0 until platelet engraftment or Day 30, whichever occurs first

† From first day with platelet count < 50 x 10^9/L until platelet engraftment or Day 30, whichever occurs first

~ Prophylactic platelets to be prescribed as per institutional practice

 # Quality of Life Assessments to be performed once a week ± 2 days

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A detailed review of the patient record, laboratory and diagnostic tests will be included during the hospitalization. Research staff will follow all patients daily for the duration of the study period. Participants will be asked to report any possible adverse events immediately. Adherence to protocol will be appraised by: 1) Nursing documentation in an inpatient setting, and 2) Self-reported Medication Adherence Form in an outpatient setting.

Patients will have their blood counts measured daily or as per institutional policy while on study. More frequent monitoring may be performed at the discretion of the treating physician.

2.6 Sample Size

As a pilot trial, the primary consideration for the sample size is the ability inform the feasibility of a full scale study. We propose a sample size of 50 adults in each treatment group for a total sample size of 100, while stratifying for participants with either myeloma or other hematologic malignancy.

2.7 Recruitment

Each site performs approximately 60 ASCT per year. Importantly, there is already an infrastructure and system in place for participating sites given that there are participating in an ongoing red cell transfusion trigger study in patients receiving a hematopoietic stem cell transplantation. Conservatively, we aim to recruit 2 patients per month at each participating site.

Methods and Analysis: Assignment of Interventions

3.1 Allocation (sequence generation, allocation concealment mechanism) and Implementation

Patients will be stratified by centre and disease (multiple myeloma versus other hematologic malignancies) given that the underlying disease may affect the bleeding risk and the most common indication for ASCT is multiple myeloma.

Further, they will then be assigned either of the transfusion strategy by block randomization to optimize balance between the 2 treatment arms. The randomization sequence will be determined by the Ottawa Methods Centre (Ottawa Hospital Research Institute) generated by computer-generated random numbers where random blocks of 2 and 4 for each participating centre will help facilitate balance.

The Ottawa Methods Centre at the Ottawa Hospital Research Institute will design and maintain web based randomization forms. The forms will contain a check list of eligibility criteria as described in Sections 2.2.1 and 2.2.2. The local investigator and/or designate will “check-off” and acknowledge patient eligibility. If all criteria are met, then randomization will be completed, and the site will be informed of the study arm assigned by email. The recipient will be considered enrolled in the trial at the time of consent.

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Selection bias will be minimized by random allocation to treatment groups and by allocation concealment. Randomization of study participants is a valid and justified method to protect against selection biases. Similarly, co-intervention and confounding would be minimized by the randomized design. The web-based computerized randomization system as described above will be used to ensure the participating centre and individuals remain unaware of the randomization sequence. Concealment of randomization prevents selection bias by ensuring that the participating centres and individuals remain unaware of the randomization sequence. Medical and research staff, and investigators, will be blinded to randomization scheme.

3.2 Blinding (masking)

An open-label design is more prone to ascertainment bias than a double blind trial. However, this should not affect the feasibility outcomes. Moreover, it would be impractical to blind participants and health care professionals to the assigned bleeding prevention strategy. Firstly, a placebo transfusion is not feasible as blinding the treating physicians would compromise safety in making clinical decisions about platelet transfusions in circumstances associated with an increased risk of bleeding. As such, a placebo medication would be impractical given that it would then be then clear which arm is receiving the prophylactic platelet transfusion strategy.

Importantly, recent clinical trials of platelet dose that have attempted to blind subjects and physicians have not been successful as the patients and clinicians were aware of allocation based on the platelet counts and the size of the platelet product.[2] Further, the standard of care requires daily knowledge of platelet count to ensure participants' overall care and safety. We will further reduce ascertainment bias by objectively grading bleeding events using the WHO and BSMS bleeding score.

Methods and Analysis: Data Collection, Management and Analysis

4.1 Data Collection methods

Information will be collected and recorded on Case Report Forms (CRF). These will be completed at study entry (registration and randomization), Day 0 (first day of stem cell infusion), and on an on-going basis until Day 30 post ASCT (or until time of death, whichever is sooner). Copies of the completed CRFs are to be submitted to the Project Management Office within 30 days of Day 0 and Day 30. The original CRFs and Questionnaires will sent to the coordinating centre. Source documentation and copies of CRFs and Questionnaires will be stored at each site.

4.2 Data management

The Ottawa Methods Centre will perform the randomization, data collection and statistical support while the multi-Centre coordinator will oversee management, site monitoring, administration and meeting support. A centralized database will be utilized and housed on a secure server with daily backup. The Multi-centre Coordinator will also communicate with data management and clinical research personnel in each of the participating institutions.

4.3 Statistical methods

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Binary/categorical endpoints will be compared between treatment groups using logistic regression. Both an "intention-to-treat" and on-protocol analysis will be performed. "Intention to treat" analysis will be supplemented by a sensitivity analysis that excludes patients who were non-compliant or loss to follow-up.

Where appropriate, analyses will employ a 2-tailed test for significance to account for the possibility that either treatment arm may be beneficial. Analysis of time-to-failure endpoints will make use of Kaplan-Meier estimates, log-rank tests, and Cox proportional hazards models as appropriate. Binary and categorical endpoints will be compared between treatment groups using logistic regression. The results for each of the endpoints will be summarized using significance tests at level of 0.05 and 95 percent confidence intervals. Analysis of secondary endpoints will be considered exploratory and hypothesis generating.

We will also perform recurrent event analysis for bleeding events as proposed by Cook et al..[18 55] Quality of Life (QOL) data will be summarized using a combination of descriptive statistics and side-by-side box plots showing distributions of scores over time. A further analysis across time points will be done using repeated-measures ANOVA and any transformation to the raw data when statistical appropriate.

All data will be analyzed centrally through the Clinical Epidemiology Program and Centre for Transfusion Research in Ottawa.

Methods and Analysis: Monitoring

5.1 Data Monitoring

The Multi-Centre Coordinator will review the protocol and CRFs with the investigator and study staff before study initiation at the site initiation visit or the investigator's meeting. A monitor will visit sites as needed throughout the duration of the study to verify the quality of data and to ensure the standards of Good Clinical Practice are being met. A monitoring plan will be developed and adhered to for the duration of the study.

During the course of the study, an independent Data Safety Monitoring Board (DSMB) will set up to review efficacy and safety data. The DSMB will consist to a Chair and 2 members. The members will have expertise in Transfusion Medicine, ASCT and Clinical Trials. The DSMB will convene after each 25 patients that are enrolled or after 6months, whichever comes first. Additional meetings/conferences calls will be conducted as necessary. The DSMB will use their experience in reviewing the data submitted to them. There will not be a formal stopping rule; the DSMB will use their experience and expertise to advise the PATH Steering Committee on the prudence of stopping the trial early due to safety concerns.

5.2 Harms

All participants are to be assessed for adverse events according to local institutional practice following standard ASCT except where additional assessment is required per protocol. Source

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documentation of adverse events should be according to institutional practice, except in cases where additional information is required to be documented by the protocol.

5.2.1 Adverse events reporting

Adverse events will be reported in the Data Collection Forms on both study arms as follows:

1. Adverse event reporting should begin on the day 0 of ASCT.
2. All adverse events of grade 3 or greater and serious adverse events will be recorded up to platelet engraftment or Day30, whichever comes first.
3. The start date of each adverse event (that meets the criteria for recording) will be recorded in the "Adverse Event Data Collection" form. The start date is defined as the date the adverse event first meets the criteria for grade 3 or greater. Stop dates do not need to be recorded unless the event is a serious adverse event (SAE) meeting the criteria for expedited reporting.
4. Abnormal laboratory results do not need to be recorded unless considered by the investigator to be relevant in terms of subject or trial safety (or in relation to a serious adverse event that is being reported). Complete Blood Counts (includes a White cell count, Hemoglobin and Platelet) are performed and reviewed during ASCT as part of routine clinical care. These values are expected to decrease as a direct consequence of the transplant procedure, which is unrelated to the red cell transfusion trigger. Consequently, we will not report any low white cell count, hemoglobin or platelet values as an adverse event**,** unless the decrease in these values is directly attributed to the Tranxaemic Acid or platelet transfusion. We will document all platelet values as this is required to establish when a platelet transfusion should occur.

5.2.2 Expedited SAE Reporting

Expedited SAE reporting are those that are deemed *unexpected* (not consistent with product information or labeling) and *related / possibly related* to the study intervention) will be faxed by the PATH Coordinating Centre to the Office of Clinical Trials, Health Canada using a) Adverse Drug Reactions (ADRs) for Clinical Trials Expedited Reporting Summary Form and b) Council for International Organizations of Medical Sciences -CIOMS form) within the following timeframes:

1. where it is neither fatal nor life-threatening, within 15 days after becoming aware of the information;
2. where it is fatal or life-threatening, immediately where possible and, in any event, within 7 days after becoming aware of the information; and
3. within 8 days after having informed Health Canada of the ADR, submit as complete a report as possible which includes an assessment of the importance and implication of any findings. (http://www.hc-sc.gc.ca/dhp-mps/prodpharma/applic-demande/guide-ld/clini/cta_post_approval-eng.php#adr)

In the case of an Expedited SAE, the PATH SAE form should be forwarded to the Central Coordinator as soon as possible after the site Research Coordinator learns of the event. Ideally,

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the Central Coordinating Centre should be apprised within 24 hours of the event. This requirement is applicable from the day of ASCT up to the end of study follow-up (either Platelet engraftment or Day 30 post-ASCT, whichever comes first).

All fields in the trial-specific SAE form will be completed. The local investigator will review, sign and date the SAE form for confirmation of its accuracy. All Institutional Review Boards (IRB) engaged in the PATH study will be informed of Expedited SAEs by the respective Site Coordinator (once the Multi-centre Coordinator has informed the site). The Multi-centre Coordinator may require further information from the site research team in order to complete the submission to Health Canada. Site research teams are requested to provide such requested information in a timely fashion.

The Study Chair and/or Study Steering Committee will review all SAE's received from the sites. If an SAE is confirmed, a document summarizing the SAE will be distributed to participating sites. Sites will follow the guidelines of their local IRB with respect to the submission of SAE's that occur at the site as well as SAE Notifications.

5.2.3 Grading of Adverse Events

The NCI Common Toxicity Criteria (CTCAE) Version 4 will be used to grade adverse events that recipients experience. A copy of version 4 of the CTCAE is available from the CTEP home page [http://ctep.info.nih.gov]

5.2.4 Reporting of Deaths

All deaths must be reported to the Project Management Office within 24 hours of the site's knowledge of the death. This requirement is applicable from the 1st day of HSCT to the end of study follow-up (Day 30 post-ASCT). Death is considered a separate SAE from the SAE that precedes the death (i.e. the SAE leading to the death). A separate Death form must be completed in addition to the SAE form.

5.3 Auditing

The investigator must give the monitor access to relevant hospital or clinical records to confirm their consistency with the CRF entries. No information in these records about the identity of the patients will leave the study centre. Monitoring standards require verification of the presence of informed consent, adherence to the inclusion/exclusion criteria, documentation of all adverse events and outcomes required as per protocol. The investigator(s)/institution(s) will permit trial-related monitoring, audits, IRB review and regulatory inspections(s), providing direct access to source data/documents.

ETHICS AND DISSEMINATION

6.1 Research ethics approval

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This study will be undertaken at a site only after IRB has given full approval of the final protocol, amendments (if any), the informed consent form(s), applicable recruiting materials, and the study management center has received a copy of this approval. This approval letter must be dated and must clearly identify the documents being approved. The study management center will require a copy of all IRB documents.

6.2 Protocol amendments

Any protocol amendments will be approved by the Steering Committee and communicated electronically to site investigators and research staff. In turn, the amended protocol will be forwarded to respective site IRBs for review. Health Canada and the online trial registry will be accordingly updated.

6.3 Consent or assent

The recipient and/or the recipient's legally authorized guardian must acknowledge in writing (consent) to become a study subject on the PATH study. Consent will be obtained jointly by the most responsible health care provider (local investigator or co-investigator) and the local research coordinator.

6.4 Confidentiality

Case Report Forms will be faxed or mailed to the Multi-Centre Coordinator's Office at registration and at follow-up time points. Data will be identified by an alphanumeric code only. Data will be entered (by staff at the Multi-Centre Coordinator's Office or Data Management Services) into the database. Importantly, source documentation will remain at their respective participating centre's site. The server for the database will be located in the Ottawa Hospital Research Institute under the care of the Methods Centre. Appropriate security measures will be in place such that current Canadian privacy laws are adhered to with respect to security and confidentiality of data, electronic data transmission, data storage and data access. A secure ID and password will be necessary to access the system. Audit trails of entries will be provided. The Project Manager and delegate will be the only individuals that can edit data. Records will be retained for a period of 25 years as per Health Canada regulations. After 25 years, all study records will be destroyed according to local policy. If the investigator withdraws from the responsibility of keeping the study records, custody must be transferred to a person willing to accept the responsibility.

Sites will track enrolment on a log where they will record the following information: patient name, hospital number, contact information, unique study number (randomization number), and study arm assigned. This log will not leave the site and will not be sent to the coordinating center. The unique study number will be used to identify all CRFs (paper) from the site to the Multi-centre Coordinator's Office. The unique study number should be used regarding any other communication between the site and the Multi-centre Coordinator's Office.

6.5 Declaration of interests

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The authors and investigators have no relevant conflicts of interests.

6.6 Access to data

The Multi-Centre Coordinator's Office (and delegate) will be the only individuals who have authorization to transfer data to the statistician for study analysis.

6.7 Ancillary and post-trial care

There will be no specific post-trial care, where medical care will follow local institutional practices. In the event of a study-related injury or illness, the participant will be provided with appropriate medical treatment and care. Financial compensation for lost wages, disability or discomfort due to an injury or illness will not be available. The legal rights of the participant will not be waived as a result of participation in the PATH. The investigators and their respective institutions will still have their legal and professional responsibilities.

6.8 Dissemination policy

Knowledge translation activities will take place throughout the duration of the study and will include clinical rounds, presentations, research team presentations at conferences, and web-based disseminations. The project is registered with ClinicalTrials.gov. Scholarly articles will be submitted to relevant journals with open access publication. At the time or writing, there is no specific plan(s) to grant public access to the full protocol, participant-level dataset, or statistical code.

ADMINISTRATIVE INFORMATION

Steering Committee

The interdisciplinary research team is composed of experienced researchers and clinicians with expertise in Stem cell transplantation, psychology and quality of life measures in transplant, transfusion medicine as well as clinical trials. The principal investigators and the co-investigators will serve as the steering committee. Independently and collectively the investigators have a wide range of expertise including transfusion medicine (AT, DS), transplantation (CB, DA, MS, DS, JT), malignant hematology (JT, DS, MS), clinical psychology and quality of life (SB), clinical trials (AT, DAF, JT, DS, KT, CB), epidemiology (DAF, AT, JT, DS, KT, CB) and economic analyses (KT).

Trial Sponsor

The PATH study is sponsored by The Ottawa Hospital Research Institute, 725 Parkdale Ave. Ottawa, Ontario, Canada, K1Y 4E9.

DISCUSSION

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Prophylactic platelet transfusions are commonly prescribed in patients undergoing ASCT to prevent bleeding based on daily measured platelet threshold (commonly < 10 x 10^9/L). However, observational studies suggest that the platelet number does not correlate with clinical significant bleeding. Moreover, recent randomized studies suggest that prophylactic transfusions may not be necessary in patients receiving ASCT. However, ASCT clinicians remain uncomfortable not providing prophylactic platelets in the presence of thrombocytopenia. The PATH pilot study will "bridge this gap" with the use of prophylactic tranexamic acid instead of prophylactic platelet transfusions.

There are several innovative features of the PATH pilot study design. Firstly, investigations will remain blinded to the data collected in this pilot study. The data will be reviewed in aggregate by the investigators while unblinded data is available to the DSMB. In this way, the patients enrolled in this pilot study can be part of the eventual sample size for the definitive phase III study. Secondly, the collection of patient reported outcomes/quality of life data is unique in clinical trials in platelet transfusions. Finally, we intend to engage patients and caregivers to better appreciate their preferences for a primary endpoint, in designing a Phase III study.

Given the resource utilization and high rate of adverse outcomes in HSCT, our study will provide the framework for better understanding the optimal use of platelet transfusions in patients receiving an ASCT. In this pilot study, we aim to determine the feasibility and logistics of conducting a multicenter trial and determine clinical outcome rates in order to plan and execute a prospective definitive randomized study.

TRIAL STATUS – MILESTONES AND CURRENT STATUS

This trial was conceived and designed in the autumn of 2014. Peer reviewed funding through the Canadian Institute of Health Research Transitional Operation Grant Competition 2014-2015 was sought in 02 March 2015 and successfully obtained on April 2015. Developments in protocol, randomization scheme, data management, case report forms, study monitoring and DSMB setup occurred between April and Dec 2015. The trial was registered on clinicaltrials.gov on 06 Jan 2016. Research Ethics Board approval at the Ottawa Health Science Network Research Ethics Board took place on 26 May 2016. We in the process of finalizing an electronic version of our case report forms and trial database management systems. We anticipate that the study will begin enrollment in Ottawa in August 2016 while HSCT centres in Calgary, Hamilton, London and Saskatoon have been approached for involvement.

COMPETING INTERESTS

The authors declare that they have no competing interests. The sponsors had no role in study design and preparation of the article, conduct of the study, and in the decision to submit the paper for publication.

ABBREVIATIONS

ADR	Adverse Drug Reactions
ASCT	Autologous Stem Cell Transplantation

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BSMS	Bleeding Severity Measurement Scale
CRF	Case Report Forms
CTCAE	Common Terminology Criteria for Adverse Events
DSMB	Data Safety Monitoring Board
IRB	Institutional Review Board
PCORI	Patient-Centered Outcomes Research Institute
PATH	Platelet Transfusions in Hematopoietic Stem cell Transplantation
SAE	Severe Adverse Event
WHO	World Health Organization

AUTHOR'S CONTRIBUTIONS

All listed authors (JT, DA, SB, CB, DF, MS, DS, KT and AT) were equally involved in the design of the study and original grant submission to the Canadian Institute of Health Research. JT is the principal investigator involved in the protocol development, "write-up" of this manuscript, execution and "day to day" management of this study. Equal input was received from all other listed authors with respect to the above activities. All authors read and approved the final manuscript.

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REFERENCES

1. Paulsen K. Canadian Blood and Marrow Transplant Group Registry. In: Sheppard D, ed., 2015.
2. Estcourt L, Stanworth S, Doree C, et al. Prophylactic platelet transfusion for prevention of bleeding in patients with haematological disorders after chemotherapy and stem cell transplantation. *Cochrane Database Syst Rev* 2012;5:CD004269. doi: 10.1002/14651858.CD004269.pub3
3. Kaufman RM, Djulbegovic B, Gernsheimer T, et al. Platelet transfusion: a clinical practice guideline from the AABB. *Ann Intern Med* 2015;162(3):205-13. doi: 10.7326/M14-1589
4. Kumar A, Mhaskar R, Grossman BJ, et al. Platelet transfusion: a systematic review of the clinical evidence. *Transfusion* 2015;55(5):1116-27; quiz 15. doi: 10.1111/trf.12943
5. Nahirniak S, Slichter SJ, Tanael S, et al. Guidance on platelet transfusion for patients with hypoproliferative thrombocytopenia. *Transfus Med Rev* 2015;29(1):3-13. doi: 10.1016/j.tmrv.2014.11.004
6. Christou G, Kekre N, Petrcich W, et al. Impact of platelet transfusion on toxicity and mortality after hematopoietic progenitor cell transplantation. *Transfusion* 2015;55(2):253-8. doi: 10.1111/trf.12817
7. Stanworth SJ, Estcourt LJ, Powter G, et al. A no-prophylaxis platelet-transfusion strategy for hematologic cancers. *N Engl J Med* 2013;368(19):1771-80. doi: 10.1056/NEJMoa1212772
8. Wandt H, Schaefer-Eckart K, Frank M, et al. A therapeutic platelet transfusion strategy is safe and feasible in patients after autologous peripheral blood stem cell transplantation. *Bone Marrow Transplant* 2006;37(4):387-92. doi: 10.1038/sj.bmt.1705246
9. Wandt H, Schaefer-Eckart K, Wendelin K, et al. Therapeutic platelet transfusion versus routine prophylactic transfusion in patients with haematological malignancies: an open-label, multicentre, randomised study. *Lancet* 2012;380(9850):1309-16. doi: 10.1016/S0140-6736(12)60689-8
10. Callum JL, Lin Y, Pinkerton PH, et al. Bloody Easy 3: Blood Transfusions, Blood Alternatives and Transfusion Reactions, A Guide to Transfusion Medicine. 3rd ed: Orbcon 2011.
11. Galel SA. Infectious Disease Screening AABB Technical Manual. 18th ed2014:179-206.
12. Lin Y, Callum JL, Pinkerton PH. Adverse Reactions. Clinical Guide To Transfusion. 2011 ed, 2013.
13. Mazzei CA, Popovsky M, Kopko PM. Noninfectious Complications of Blood Transfusion In: Fung M, Grossman BJ, Hillyer C, et al., eds. AABB Technical Manual2014:665-92.
14. Wardrop D, Estcourt LJ, Brunskill SJ, et al. Antifibrinolytics (lysine analogues) for the prevention of bleeding in patients with haematological disorders. *Cochrane Database Syst Rev* 2013;7:CD009733. doi: 10.1002/14651858.CD009733.pub2
15. Avvisati G, ten Cate JW, Buller HR, et al. Tranexamic acid for control of haemorrhage in acute promyelocytic leukaemia. *Lancet* 1989;2(8655):122-4.
16. Shpilberg O, Blumenthal R, Sofer O, et al. A controlled trial of tranexamic acid therapy for the reduction of bleeding during treatment of acute myeloid leukemia. *Leuk Lymphoma* 1995;19(1-2):141-4. doi: 10.3109/10428199509059668

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17. Stanworth SJ, Estcourt LJ, Llewelyn CA, et al. Impact of prophylactic platelet transfusions on bleeding events in patients with hematologic malignancies: a subgroup analysis of a randomized trial. *Transfusion* 2014;54(10):2385-93. doi: 10.1111/trf.12646
18. Heddle NM, Cook RJ, Tinmouth A, et al. A randomized controlled trial comparing standard- and low-dose strategies for transfusion of platelets (SToP) to patients with thrombocytopenia. *Blood* 2009;113(7):1564-73. doi: 10.1182/blood-2008-09-178236
19. Slichter SJ, Kaufman RM, Assmann SF, et al. Dose of prophylactic platelet transfusions and prevention of hemorrhage. *N Engl J Med* 2010;362(7):600-13. doi: 10.1056/NEJMoa0904084
20. Tinmouth A, Tannock IF, Crump M, et al. Low-dose prophylactic platelet transfusions in recipients of an autologous peripheral blood progenitor cell transplant and patients with acute leukemia: a randomized controlled trial with a sequential Bayesian design. *Transfusion* 2004;44(12):1711-9. doi: 10.1111/j.0041-1132.2004.04118.x
21. Sensebe L, Giraudeau B, Bardiaux L, et al. The efficiency of transfusing high doses of platelets in hematologic patients with thrombocytopenia: results of a prospective, randomized, open, blinded end point (PROBE) study. *Blood* 2005;105(2):862-4. doi: 10.1182/blood-2004-05-1841
22. Bredeson C. President of Canadian Blood and Marrow Transplant Group. In: Sheppard D, ed., 2015.
23. Gaydos LA, Freireich EJ, Mantel N. The quantitative relation between platelet count and hemorrhage in patients with acute leukemia. *N Engl J Med* 1962;266:905-9. doi: 10.1056/NEJM196205032661802
24. Friedmann AM, Sengul H, Lehmann H, et al. Do basic laboratory tests or clinical observations predict bleeding in thrombocytopenic oncology patients? A reevaluation of prophylactic platelet transfusions. *Transfus Med Rev* 2002;16(1):34-45.
25. Bernstein SH, Nademanee AP, Vose JM, et al. A multicenter study of platelet recovery and utilization in patients after myeloablative therapy and hematopoietic stem cell transplantation. *Blood* 1998;91(9):3509-17.
26. Stanworth SJ, Hyde C, Brunskill S, et al. Platelet transfusion prophylaxis for patients with haematological malignancies: where to now? *Br J Haematol* 2005;131(5):588-95. doi: 10.1111/j.1365-2141.2005.05769.x
27. Schiffer CA, Anderson KC, Bennett CL, et al. Platelet transfusion for patients with cancer: clinical practice guidelines of the American Society of Clinical Oncology. *J Clin Oncol* 2001;19(5):1519-38.
28. Higby DJ, Cohen E, Holland JF, et al. The prophylactic treatment of thrombocytopenic leukemic patients with platelets: a double blind study. *Transfusion* 1974;14(5):440-6.
29. Murphy S, Litwin S, Herring LM, et al. Indications for platelet transfusion in children with acute leukemia. *Am J Hematol* 1982;12(4):347-56.
30. Solomon J, Bofenkamp T, Fahey JL, et al. Platelet prophylaxis in acute non-lymphoblastic leukaemia. *Lancet* 1978;1(8058):267.
31. Blumberg N, Heal JM, Liesveld JL, et al. Platelet transfusion and survival in adults with acute leukemia. *Leukemia* 2008;22(3):631-5. doi: 10.1038/sj.leu.2404920
32. Eftekharian H, Vahedi R, Karagah T, et al. Effect of tranexamic acid irrigation on perioperative blood loss during orthognathic surgery: a double-blind, randomized controlled clinical trial. *J Oral Maxillofac Surg* 2015;73(1):129-33. doi: 10.1016/j.joms.2014.07.033

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33. Karaaslan F, Karaoglu S, Mermerkaya MU, et al. Reducing blood loss in simultaneous bilateral total knee arthroplasty: combined intravenous-intra-articular tranexamic acid administration. A prospective randomized controlled trial. *Knee* 2015;22(2):131-5. doi: 10.1016/j.knee.2014.12.002
34. Mirghafourvand M, Mohammad-Alizadeh S, Abbasalizadeh F, et al. The effect of prophylactic intravenous tranexamic acid on blood loss after vaginal delivery in women at low risk of postpartum haemorrhage: a double-blind randomised controlled trial. *Aust N Z J Obstet Gynaecol* 2015;55(1):53-8. doi: 10.1111/ajo.12262
35. Roberts I, Coats T, Edwards P, et al. HALT-IT--tranexamic acid for the treatment of gastrointestinal bleeding: study protocol for a randomised controlled trial. *Trials* 2014;15:450. doi: 10.1186/1745-6215-15-450
36. Sprigg N, Renton CJ, Dineen RA, et al. Tranexamic acid for spontaneous intracerebral hemorrhage: a randomized controlled pilot trial (ISRCTN50867461). *J Stroke Cerebrovasc Dis* 2014;23(6):1312-8. doi: 10.1016/j.jstrokecerebrovasdis.2013.11.007
37. Zehtabchi S, Abdel Baki SG, Falzon L, et al. Tranexamic acid for traumatic brain injury: a systematic review and meta-analysis. *Am J Emerg Med* 2014;32(12):1503-9. doi: 10.1016/j.ajem.2014.09.023
38. National Heart Lung and Blood Institute. The diagnosis, evaluation, and management of von Willebrand disease. NIH publication no 08-5832. Bethesda, MD: U.S. Dept. of Health and Human Services, National Institutes of Health, National Heart, Lung, and Blood Institute,, 2007.
39. Srivastava A, Brewer AK, Mauser-Bunschoten EP, et al. Guidelines for the management of hemophilia. *Haemophilia* 2013;19(1):e1-47. doi: 10.1111/j.1365-2516.2012.02909.x
40. World Health Organization. WHO handbook for reporting results of cancer treatment. Geneva: World Health Organization 1979.
41. Bercovitz RS, O'Brien SH. Measuring bleeding as an outcome in clinical trials of prophylactic platelet transfusions. *Hematology Am Soc Hematol Educ Program* 2012;2012:157-60. doi: 10.1182/asheducation-2012.1.157
42. Koreth R, Weinert C, Weisdorf DJ, et al. Measurement of bleeding severity: a critical review. *Transfusion* 2004;44(4):605-17. doi: 10.1111/j.1537-2995.2004.03153.x
43. Estcourt LJ, Heddle N, Kaufman R, et al. The challenges of measuring bleeding outcomes in clinical trials of platelet transfusions. *Transfusion* 2013;53(7):1531-43. doi: 10.1111/trf.12058
44. Webert K, Cook RJ, Sigouin CS, et al. The risk of bleeding in thrombocytopenic patients with acute myeloid leukemia. *Haematologica* 2006;91(11):1530-7.
45. Webert KE, Arnold DM, Lui Y, et al. A new tool to assess bleeding severity in patients with chemotherapy-induced thrombocytopenia. *Transfusion* 2012;52(11):2466-74; quiz 65. doi: 10.1111/j.1537-2995.2012.03634.x
46. Estcourt LJ, Pinchon D, Symington E, et al. Does bleeding affect patient-reported outcome measures in patients with myelodysplasia or hematologic malignancies: a systematic review. *Transfusion* 2014;54(4):1166-79. doi: 10.1111/trf.12441
47. Heddle NM, Arnold DM, Webert KE. Time to rethink clinically important outcomes in platelet transfusion trials. *Transfusion* 2011;51(2):430-4. doi: 10.1111/j.1537-2995.2010.02982.x
48. Rabin R, de Charro F. EQ-5D: a measure of health status from the EuroQol Group. *Ann Med* 2001;33(5):337-43.

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49. Cella D, Beaumont JL, Webster KA, et al. Measuring the concerns of cancer patients with low platelet counts: the Functional Assessment of Cancer Therapy--thrombocytopenia (FACT-Th) questionnaire. *Support Care Cancer* 2006;14(12):1220-31. doi: 10.1007/s00520-006-0102-1
50. Patient-Centered Outcomes Research Institute 2015 [Available from: http://www.pcori.org/ accessed 05 Nov 2015 2015.
51. Estcourt LJ, Heddle N, Kaufman R, et al. The challenges of measuring bleeding outcomes in clinical trials of platelet transfusions. *Transfusion* 2013;53(7):1531-43. doi: 10.1111/trf.12058
52. Bearman SI, Appelbaum FR, Buckner CD, et al. Regimen-related toxicity in patients undergoing bone marrow transplantation. *J Clin Oncol* 1988;6(10):1562-8.
53. McQuellon RP, Russell GB, Cella DF, et al. Quality of life measurement in bone marrow transplantation: development of the Functional Assessment of Cancer Therapy-Bone Marrow Transplant (FACT-BMT) scale. *Bone Marrow Transplant* 1997;19(4):357-68. doi: 10.1038/sj.bmt.1700672
54. Spitzer RL, Kroenke K, Williams JB, et al. A brief measure for assessing generalized anxiety disorder: the GAD-7. *Arch Intern Med* 2006;166(10):1092-7. doi: 10.1001/archinte.166.10.1092
55. Cook RJ, Heddle NM, Rebulla P, et al. Methods for the analysis of bleeding outcomes in randomized trials of PLT transfusion triggers. *Transfusion* 2004;44(8):1135-42. doi: 10.1111/j.1537-2995.2004.03231.x

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SPIRIT 2013 Checklist: Recommended items to address in a clinical trial protocol and related documents*

Section/item	Item No	Description	Addressed on page number
Administrative information			
Title	1	Descriptive title identifying the study design, population, interventions, and, if applicable, trial acronym	1
Trial registration	2a	Trial identifier and registry name. If not yet registered, name of intended registry	2
	2b	All items from the World Health Organization Trial Registration Data Set	1-24
Protocol version	3	Date and version identifier	1
Funding	4	Sources and types of financial, material, and other support	19
Roles and responsibilities	5a	Names, affiliations, and roles of protocol contributors	1 & 21
	5b	Name and contact information for the trial sponsor	18
	5c	Role of study sponsor and funders, if any, in study design; collection, management, analysis, and interpretation of data; writing of the report; and the decision to submit the report for publication, including whether they will have ultimate authority over any of these activities	19 - 20
	5d	Composition, roles, and responsibilities of the coordinating centre, steering committee, endpoint adjudication committee, data management team, and other individuals or groups overseeing the trial, if applicable (see Item 21a for data monitoring committee)	14 & 20

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Introduction			
Background and rationale	6a	Description of research question and justification for undertaking the trial, including summary of relevant studies (published and unpublished) examining benefits and harms for each intervention	3 - 8
	6b	Explanation for choice of comparators	6 - 8
Objectives	7	Specific objectives or hypotheses	8
Trial design	8	Description of trial design including type of trial (eg, parallel group, crossover, factorial, single group), allocation ratio, and framework (eg, superiority, equivalence, noninferiority, exploratory)	8
Methods: Participants, interventions, and outcomes			
Study setting	9	Description of study settings (eg, community clinic, academic hospital) and list of countries where data will be collected. Reference to where list of study sites can be obtained	8
Eligibility criteria	10	Inclusion and exclusion criteria for participants. If applicable, eligibility criteria for study centres and individuals who will perform the interventions (eg, surgeons, psychotherapists)	8 - 9
Interventions	11a	Interventions for each group with sufficient detail to allow replication, including how and when they will be administered	9 - 10
	11b	Criteria for discontinuing or modifying allocated interventions for a given trial participant (eg, drug dose change in response to harms, participant request, or improving/worsening disease)	9
	11c	Strategies to improve adherence to intervention protocols, and any procedures for monitoring adherence (eg, drug tablet return, laboratory tests)	12
	11d	Relevant concomitant care and interventions that are permitted or prohibited during the trial	10
Outcomes	12	Primary, secondary, and other outcomes, including the specific measurement variable (eg, systolic blood pressure), analysis metric (eg, change from baseline, final value, time to event), method of aggregation (eg, median, proportion), and time point for each outcome. Explanation of the clinical relevance of chosen efficacy and harm outcomes is strongly recommended	10 - 11
Participant timeline	13	Time schedule of enrolment, interventions (including any run-ins and washouts), assessments, and visits for participants. A schematic diagram is highly recommended (see Figure)	11 - 12 & Table 4

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Sample size	14	Estimated number of participants needed to achieve study objectives and how it was determined, including clinical and statistical assumptions supporting any sample size calculations	12
Recruitment	15	Strategies for achieving adequate participant enrolment to reach target sample size	12
Methods: Assignment of interventions (for controlled trials)			
Allocation:			
Sequence generation	16a	Method of generating the allocation sequence (eg, computer-generated random numbers), and list of any factors for stratification. To reduce predictability of a random sequence, details of any planned restriction (eg, blocking) should be provided in a separate document that is unavailable to those who enrol participants or assign interventions	12
Allocation concealment mechanism	16b	Mechanism of implementing the allocation sequence (eg, central telephone; sequentially numbered, opaque, sealed envelopes), describing any steps to conceal the sequence until interventions are assigned	12
Implementation	16c	Who will generate the allocation sequence, who will enrol participants, and who will assign participants to interventions	12
Blinding (masking)	17a	Who will be blinded after assignment to interventions (eg, trial participants, care providers, outcome assessors, data analysts), and how	13
	17b	If blinded, circumstances under which unblinding is permissible, and procedure for revealing a participant's allocated intervention during the trial	13
Methods: Data collection, management, and analysis			
Data collection methods	18a	Plans for assessment and collection of outcome, baseline, and other trial data, including any related processes to promote data quality (eg, duplicate measurements, training of assessors) and a description of study instruments (eg, questionnaires, laboratory tests) along with their reliability and validity, if known. Reference to where data collection forms can be found, if not in the protocol	13
	18b	Plans to promote participant retention and complete follow-up, including list of any outcome data to be collected for participants who discontinue or deviate from intervention protocols	13

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Data management	19	Plans for data entry, coding, security, and storage, including any related processes to promote data quality (eg, double data entry; range checks for data values). Reference to where details of data management procedures can be found, if not in the protocol	13
Statistical methods	20a	Statistical methods for analysing primary and secondary outcomes. Reference to where other details of the statistical analysis plan can be found, if not in the protocol	13 - 14
	20b	Methods for any additional analyses (eg, subgroup and adjusted analyses)	13- 14
	20c	Definition of analysis population relating to protocol non-adherence (eg, as randomised analysis), and any statistical methods to handle missing data (eg, multiple imputation)	13 -14
Methods: Monitoring			
Data monitoring	21a	Composition of data monitoring committee (DMC); summary of its role and reporting structure; statement of whether it is independent from the sponsor and competing interests; and reference to where further details about its charter can be found, if not in the protocol. Alternatively, an explanation of why a DMC is not needed	14
	21b	Description of any interim analyses and stopping guidelines, including who will have access to these interim results and make the final decision to terminate the trial	14
Harms	22	Plans for collecting, assessing, reporting, and managing solicited and spontaneously reported adverse events and other unintended effects of trial interventions or trial conduct	14 - 15
Auditing	23	Frequency and procedures for auditing trial conduct, if any, and whether the process will be independent from investigators and the sponsor	14-16
Ethics and dissemination			
Research ethics approval	24	Plans for seeking research ethics committee/institutional review board (REC/IRB) approval	16 & 19
Protocol amendments	25	Plans for communicating important protocol modifications (eg, changes to eligibility criteria, outcomes, analyses) to relevant parties (eg, investigators, REC/IRBs, trial participants, trial registries, journals, regulators)	16 & 19

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Consent or assent	26a	Who will obtain informed consent or assent from potential trial participants or authorised surrogates, and how (see Item 32)	17
	26b	Additional consent provisions for collection and use of participant data and biological specimens in ancillary studies, if applicable	17
Confidentiality	27	How personal information about potential and enrolled participants will be collected, shared, and maintained in order to protect confidentiality before, during, and after the trial	17
Declaration of interests	28	Financial and other competing interests for principal investigators for the overall trial and each study site	17
Access to data	29	Statement of who will have access to the final trial dataset, and disclosure of contractual agreements that limit such access for investigators	18
Ancillary and post-trial care	30	Provisions, if any, for ancillary and post-trial care, and for compensation to those who suffer harm from trial participation	18
Dissemination policy	31a	Plans for investigators and sponsor to communicate trial results to participants, healthcare professionals, the public, and other relevant groups (eg, via publication, reporting in results databases, or other data sharing arrangements), including any publication restrictions	18
	31b	Authorship eligibility guidelines and any intended use of professional writers	18
	31c	Plans, if any, for granting public access to the full protocol, participant-level dataset, and statistical code	18
Appendices			
Informed consent materials	32	Model consent form and other related documentation given to participants and authorised surrogates	NA
Biological specimens	33	Plans for collection, laboratory evaluation, and storage of biological specimens for genetic or molecular analysis in the current trial and for future use in ancillary studies, if applicable	NA

*It is strongly recommended that this checklist be read in conjunction with the SPIRIT 2013 Explanation & Elaboration for important clarification on the items. Amendments to the protocol should be tracked and dated. The SPIRIT checklist is copyrighted by the SPIRIT Group under the Creative Commons "Attribution-NonCommercial-NoDerivs 3.0 Unported" license.

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