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2015 Proceedings of the National Heart, Lung, and Blood Institute's State of the Science in Transfusion Medicine Symposium

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Abstract

On March 25-26, 2015, the National Heart, Lung, and Blood Institute sponsored a meeting on the State of the Science in Transfusion Medicine on the NIH campus in Bethesda, MD, which was attended by a diverse group of 330 registrants. The meeting's goal was to identify important research questions that could be answered in the next 5-10 years, and which would have the potential to transform the clinical practice of transfusion medicine. These questions could be

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addressed by basic, translational, and/or clinical research studies and were focused on four areas: the three “classical” transfusion products (i.e., red blood cells, platelets, and plasma) and blood donor issues. Prior to the meeting, four Working Groups, one for each area, prepared five major questions for discussion along with a list of 5-10 additional questions for consideration. At the meeting itself, all of these questions, and others, were discussed in Keynote lectures, small group breakout sessions, and large group sessions with open discourse involving all meeting attendees. In addition to the final lists of questions, provided herein, the meeting attendees identified multiple overarching, cross-cutting themes that addressed issues common to all four areas; the latter are also provided. It is anticipated that addressing these scientific priorities, with careful attention to the overarching themes, will inform funding priorities developed by the NIH and provide a solid research platform for transforming the future practice of transfusion medicine.

Keywords

Red blood cells; platelets; plasma products; blood donors

Introduction

On March 25-26, 2015, the National Heart, Lung, and Blood Institute (NHLBI) sponsored a meeting on the State of the Science in Transfusion Medicine on the NIH campus in Bethesda, MD. The goal of this meeting was to identify important research questions that could be answered in the next 5-10 years, and which would have the potential to transform the clinical practice of transfusion medicine. These questions could be addressed by basic, translational, and/or clinical research studies and were focused on four areas: the three “classical” transfusion products (i.e., red blood cells, platelets, and plasma) and blood donor issues. Prior to the meeting, four Working Groups, one for each area, prepared five major questions for discussion along with a list of 5-10 additional questions for consideration. The meeting was attended by 330 registrants representing multiple stakeholders, including academic medicine, clinicians, blood operators, the commercial sector, and government.

Presentations and Discussions

The sessions for each of the four overarching areas included a keynote address, a presentation of the Working Group's proposed questions, a breakout group session to discuss the proposed questions as well as elicit other scientific priorities, and an open and thoughtful discussion of all potential key research questions by all attendees.

We present below the five most compelling scientific priorities that emerged at the end of the 2-day discussions for each of the four major areas. Additional key research questions for each area are presented in the Appendix.

Red Blood Cells (RBCs)

What determines which individuals will develop RBC alloimmune responses resulting in clinically meaningful sequelae?

Exposure to RBC alloantigens, following transfusion or following exposure to fetal RBCs during pregnancy, can generate humoral alloantibodies capable of producing hemolytic transfusion reactions, (HTRs) or hemolytic disease of the fetus or newborn (HDFN).^{1,2} Why some patients mount detectable alloantibody responses (i.e., “responders”), whereas others do not (“non-responders”), is poorly understood.³ Among responders, alloantibodies are categorized as “clinically significant” or “clinically insignificant,” based on whether the resulting specific alloantibodies were previously reported to cause HTRs or HDFN.⁴ Key areas of investigation to be addressed include: 1) the generation of alloantibodies that limit the availability of compatible blood or cause HDFN; 2) distinguishing between clinically significant and insignificant alloantibody responses, especially for specificities known to be potentially hemolytic; 3) the biology of hyperhemolysis in patients with sickle cell disease; and 4) therapeutic interventions to prevent and/or mitigate RBC alloimmunization and its sequelae, including those involving the donor, the recipient, or the RBCs themselves.⁵

Can the potency and/or safety of transfusable RBCs be improved?

RBCs undergo changes during collection, manipulation, and storage that may reduce their potency or safety. Novel technologies may mitigate the storage lesion through new ways to process/prepare RBCs for transfusion.⁶ Both pre-clinical and clinical studies should define optimal combinations of known factors for preserving RBCs (e.g., osmolarity, energy sources, antioxidants), and develop methods for pathogen reduction that do not exacerbate the RBC storage lesion.⁷ Use of *ex vivo*-generated RBCs is an alternative to conventional donor-derived RBCs, which may improve product consistency and safety, and reduce the storage lesion.⁸ Although blood substitutes and blood “pharming” from stem cells will likely require years of development, it is now technically feasible using hematopoietic stem/progenitor cells.^{9,10} Near-term applications for special patient populations could include RBCs from rare donors for chronically transfused patients.

Are there specific conditions where a liberal RBC transfusion strategy results in lower rates of 30-day mortality as compared to a restrictive transfusion strategy?

Clinical trials show that in multiple patient populations, a 7-8 g/dL hemoglobin threshold is safe.¹¹ However, equipoise for transfusion thresholds persists in patients with ischemic heart disease and acute neurological conditions where a higher hemoglobin level may decrease injury to myocardial and cerebral tissues, respectively.¹² In other populations, transfusion thresholds lower than 7 g/dL may be safely tolerated.¹³ Alternatively, if a 7 g/dL threshold were proven superior to a lower hemoglobin level, this level would establish a minimal appropriate threshold to initiate RBC transfusion. Multicenter clinical trials using markers of oxygen consumption will be needed to answer these questions; some pilot studies have demonstrated the feasibility of recruitment for clinical scenarios in which equipoise exists. An international setting, where blood supply safety and availability are significant issues, may be best suited to answer the question of whether transfusion thresholds lower than 7 g/dL are safe. In addition to evaluating the safety of lower transfusion threshold triggers in

select patient populations, other outcome measures should be incorporated into clinical trials. Clinical trials in oncology patients were highlighted, as RBC transfusion practice has not been well studied within this population and there is some evidence that higher RBC levels enhance platelet function in thrombocytopenic patients

What are the optimal RBC transfusion thresholds for adult and pediatric cancer patients undergoing chemotherapy that may improve functional status and quality of life?

Cancer patients undergo intensive therapies, often requiring many transfusions of RBCs and other blood components for support through a period of hypoproliferative anemia to maintain their functional status. RBC transfusion has been associated with a greater risk of infection, a common cause of death in patients with hematological malignancies.¹⁴ Conversely, restrictive transfusion practice could adversely affect their quality of life (QoL) and functional status, and enhance bleeding in the setting of thrombocytopenia.^{15,16} Multicenter studies of RBC transfusion are feasible using randomized controlled designs in conjunction with clinical trials of chemotherapeutic regimens.¹⁷ Clinically relevant end points include: 1) QoL and functional status; 2) neurocognitive development in pediatric populations; 3) bleeding events; 4) impact on immunomodulation and infection; 5) reconstitution of hematopoiesis; and 6) survival and/or disease recurrence.

In patients with critical illness, what is the best means to identify the degree to which anemia contributes to insufficient oxygen (O₂) delivery and the likelihood that O₂ delivery will be improved by RBC transfusion?

Although RBC transfusion increases hemoglobin levels, it does not necessarily follow that O₂ delivery to tissues is increased.¹⁸ Restrictive thresholds for RBC transfusion are increasingly appreciated to be non-inferior to liberal thresholds for most conditions, resulting in re-consideration of the hemoglobin trigger itself.^{19,20} Ideally, RBC transfusion decisions should be based on the degree to which anemia contributes to tissue O₂ delivery.²¹ Therefore, it is important to identify physiologic endpoints for specific outcomes in order to determine the appropriate transfusion thresholds to achieve these goals. This objective requires improving current ways of assessing functionality of the circulating RBC mass and its relationship to tissue O₂ delivery. Clinical practice may ultimately be improved by: 1) examining physiologic tolerance of anemia; 2) evaluating the transfusion decision-making process in critical illness; and 3) exploring novel approaches to quantify and monitor O₂ consumption and delivery to determine their relationship to patient outcomes.²²

Platelets

How safe and effective are prophylactic platelet transfusions before common invasive procedures in preventing bleeding?³²⁻³⁴

The efficacy and risks of prophylactic platelet transfusions to thrombocytopenic patients before common invasive procedures (e.g., liver biopsy, intravenous catheter insertion, lumbar puncture) are largely unknown. With little data, decisions to transfuse are frequently made following institutional guidelines that are not evidence-based and may be designed to address perceived litigation risks. Bleeding risk and potential adverse effects of transfusion may differ dramatically between patients, but transfusion thresholds are frequently the same.

The contribution of platelet transfusion to inflammation and organ injury may be considerable and depend on individual physiology. How these factors may impact infection, organ dysfunction, and long-term outcomes is unclear. Randomized clinical trials evaluating different transfusion thresholds with objective clinical outcome measurements could include parallel validation of *in vitro* measurements of platelet function, hemostasis, and thrombosis. Measuring inflammatory markers could help explain the pathogenesis of adverse effects and identify patients at risk.

How should platelet transfusions be used to treat active bleeding?²⁵⁻²⁸

No high-quality evidence guides platelet transfusions in patients with active bleeding. Platelet count is almost always the sole laboratory result considered when deciding to transfuse platelets, but provides no information about platelet function and contribution to bleeding. Test-based transfusion algorithms, including the use of viscoelastic test methods (see below), may reduce blood product utilization, but there are no standards for laboratory or clinical assessment of hemostatic efficacy of platelets transfused for active bleeding. It is critical to conduct clinical trials that validate clinical bleeding measurements, evaluate the usefulness of *in vitro* testing, and assess the adverse effects of platelet transfusion. Routine platelet transfusions to bleeding medical and surgical patients provide extensive opportunities to conduct clinical studies in pediatric and adult settings, to improve understanding of the underlying pathophysiology of bleeding, broadly and in individuals, and to best utilize available resources.

What new methods of platelet preparation, processing, and storage must be developed to meet safety and hemostatic needs of patients in various clinical situations?²⁸⁻³⁰

Limitations of 5-day, 22°C storage significantly impacts platelet availability. It is critical that new methods of collection, processing, and storage be developed to extend platelet storage time, including using whole blood and evaluating the suitability of cold storage. Understanding which attributes of these products are necessary for optimal alignment with efficacy and safety in specific clinical situations is also required. Platelet transfusion alone does not prevent bleeding; the overall state of hemostasis and endothelium, and donor characteristics affecting platelet quality, may be important in selecting the best product. Better laboratory and clinical measurements of platelet function, efficacy, and safety are essential. Outcomes should link *in vitro* testing, results in animal models, and clinical effects, such as hemostasis, thrombosis, immunity, and endothelial integrity. Recipient (e.g., immune, platelet, or endothelial dysfunction), donor, and platelet preparation characteristics should be systematically analyzed and include considerations of glycomics, metabolomics, proteomics, genomics, *in vivo* microscopy, and advanced imaging.

What are the knowledge and technological gaps in production, evaluation, and clinical translation of donor-independent platelets for transfusion?^{31,32}

Platelets produced from induced pluripotent stem or progenitor (i.e., megakaryocyte) cells (“biologic production”) or manufactured from engineered biomaterials (“synthetic production”) could address supply issues and transfusion-related function and safety concerns. One important step is improving stem and progenitor cell expansion in culture.

Another goal is to develop synthetic platelet mimetics using biomaterials engineering. Hemostatic efficacy and safety of these products must be established in clinically-relevant models and patients. Approaches include: establishing high throughput screens for compounds that expand CD34 or CD41 cells or trigger platelet release and ploidy, developing culture methods using 3D scaffolds to mimic the bone marrow niche, and using proteomics or RNA-sequencing to identify molecules critical for terminal megakaryocyte maturation and platelet formation. Large-scale bioreactors can be adapted to test molecules, triggers, and conditions for amplifying platelet production. Large-scale platelet production by biologic and synthetic routes would enable studies in animal models with clinically relevant bleeding disorders to correlate design and dosage with hemostatic function and safety.

What are the clinical and immunologic consequences of ABO or Rh type specific vs. non-type specific platelet transfusions?³³⁻³⁶

Practices for ABO and Rh matching of platelets for transfusion vary widely. ABO non-identical platelets are associated with increased platelet refractoriness, RBC transfusion needs and hemolysis, organ injury, transfusion reactions, and mortality. How Rh or other blood group alloimmunization influence outcomes of cardiac surgery, massive transfusion, and hematopoietic stem cell engraftment is unknown. The effects of ABO immune complexes on endothelial cells, glycan interactions with cells of the vasculature and blood, and how these are modulated by interaction with Toll-like receptors, interleukin receptors, and other secreted cytokines require study. Because many patients receive platelet transfusions for stem cell transplantation, cardiac surgery, and trauma, randomized trials comparing clinical outcomes of ABO and Rh matching are feasible, and will allow study *in vitro* and *in vivo* of the effects on inflammation, adaptive/innate immunity, hemostasis, and thrombosis.

Plasma

In critically ill patients undergoing invasive procedures, at what International Normalized Ratio (INR) does prophylactic plasma transfusion prevent bleeding complications and improve patient outcomes?³⁷

Clinical studies that evaluate the best strategies for plasma transfusion strategies are lacking. Thus, despite this deficiency of high quality evidence, prophylactic administration of plasma triggered by the INR continues to drive plasma transfusion in critical care. Coagulation test abnormalities are common in Intensive Care Units (ICUs) and plasma is frequently administered for this reason prior to procedures. Therefore, adequately sized study populations for multicenter trials are feasible. Relevant outcomes should include procedural bleeding complications, transfusion requirements, transfusion-related complications, and measures of healthcare resource utilization. To improve clinical trial feasibility, novel designs may prove desirable. For example, an adaptive trial design where sequential increases in INR threshold are used for randomization would allow information obtained in the early portion of the trial to inform the merit, feasibility, and safety of continuation (Figure 1).

Does using viscoelastic testing to guide plasma transfusion improve outcomes when compared with traditional coagulation testing?³⁸⁻⁴⁰

The INR, activated Partial Thromboplastin Time (aPTT), and platelet count frequently guide hemostatic interventions, particularly in the ICU. However, these tests may be poor predictors of coagulopathy or bleeding in various clinical settings. Recently, renewed interest in viscoelastic tests (e.g., thromboelastography/rotational thromboelastometry) has emerged as alternative assessments of coagulation and guides to blood component use. Indeed, a body of literature supports their potential value in specific clinical settings, such as liver transplantation and cardiac surgery. However, uncertainty exists over the relative value of these different testing strategies in ICU patients. Because coagulation testing and associated plasma transfusion occur daily in ICUs worldwide, enrolling adequately-sized study populations in multi-center trials appears feasible. Endpoints should include relevant clinical outcomes (e.g., mortality, bleeding complications, adverse effects) and resource utilization (e.g., total blood products consumed, hospital length of stay, fixed and variable testing costs). To improve feasibility, efficiency, and cost of these types of trials, novel study designs (e.g., a stepped wedge cluster randomized trial) should be considered.

For ICU patients with coagulopathy and World Health Organization Grade 3 or 4 bleeding, which hemostatic therapy is preferred?⁴¹⁻⁴³

Bleeding is frequently encountered in the ICU and is associated with substantial morbidity and mortality. When bleeding occurs, coagulopathy is often present and the optimal therapeutic approach remains debatable; for example, the benefits and risks of 4-factor prothrombin complex concentrate (PCC) versus plasma remain poorly understood. As coagulopathy and associated bleeding are common in the ICU, multicenter clinical trials evaluating this knowledge gap are feasible. Relevant endpoints should include: hemostatic efficacy, adverse events (e.g., Transfusion-Associated Circulatory Overload, thrombosis), additional important patient outcomes, and healthcare resource utilization.

Would development of a concentrated plasma product provide comparable hemostatic efficacy and improved safety compared with traditional plasma?

A major impetus underlying the growth of clotting factor concentrates stems from the perceived value of reduced volume and enhanced speed of administration. Nonetheless, a full plasma concentrate would provide balanced replacement of all circulating plasma proteins. Thus, successful development and clinical testing of concentrated plasma could provide a cost-effective alternative to recombinant or plasma-derived factor concentrates, and could find broad application in treating coagulopathy. Several strategies have already been explored to develop concentrated plasma, including freeze-drying,⁴⁴ lyophilization,⁴⁵ and spray-drying plasma followed by reconstitution in sterile water.⁴⁶ The US Military also has experience with concentrated plasma products produced in other countries. Therefore, further development of a concentrated plasma product is feasible.

For rapidly bleeding, surgical (non-trauma) patients, which hemostatic resuscitation strategy (i.e., goal-directed versus ratio-based) is superior?

Coagulopathy frequently develops in the setting of massive surgical hemorrhage and the optimal treatment strategy remains unknown. In addition, existing randomized trials in trauma patients may not be generalizable to non-trauma settings.^{47,48} Moreover, direct comparisons between goal-directed and fixed-ratio plasma transfusion approaches have not been performed. To optimize feasibility, targeted enrollment of surgical patients with increased risk of hemorrhage should be considered. Similarly, implementing predictive algorithms (e.g., a critical RBC administration threshold) may improve subject recruitment. With these strategies, an adequately sized study population is expected in a multicenter clinical trial. Endpoints include hemostatic efficacy, other clinical outcomes (e.g., mortality), and healthcare resource utilization. Use of novel clinical trial designs (e.g., stepped wedge cluster randomized trials) should be considered.

Donor Issues

Is a risk-based framework possible for evaluating the blood donor selection process, to capture relevant risk factors for transfusion-transmitted diseases, while modifying policies that do not contribute to transfusion safety?

Precautionary measures are critical to blood safety, but the “precautionary principle” requires periodic evaluation of donor selection policies as information accumulates on risk, benefit, and cost. Deferral policies for behavioral risk factors often differ among countries. After considerable deliberation and further research, the US FDA released a draft guidance document in May 2015 to recommend changing the deferral period for men who have had sex with men from an indefinite period to one year.⁴⁹ A framework is needed to evaluate other blood donor deferral policies to identify relevant risk factors among prospective donors, and modify those questions that do not contribute to blood safety.⁵⁰ In addition, factors that influence blood donors' compliance and comprehension of the educational material and questions are incompletely characterized, but strongly influence the effectiveness of the screening process and the validity of the information elicited by the questionnaire. Blood centers have successfully collaborated on pilot and exploratory studies to define, collect, and analyze specific data to evaluate blood donor eligibility criteria. Rational and prudent donor selection, deferral, and retrieval policies are crucial to protect transfusion recipients while encouraging repeat blood donation among healthy, motivated individuals.

What biochemical and physiological responses to acute blood and iron loss occur during blood donation?

Whole blood donation rapidly removes ~10% of total blood volume within ~15 minutes, providing a unique opportunity to examine how biochemical pathways regulating iron metabolism and hemoglobin biosynthesis respond to acute hemorrhage in otherwise healthy individuals.⁵¹ Studies could examine the impact of genetic polymorphisms of iron regulation and hemoglobin biosynthesis, on physiological responses to blood donation and recovery from blood donation, and on mechanisms affecting dietary iron absorption. Blood donor diversity would enable research into genetic determinants of the racial variability in the

hemoglobin set point and the changes in biochemical responses with aging. These studies in healthy individuals may also help us to understand disease mechanisms and treatments for anemia, inflammation, iron overload, bone marrow expansion/bone health, infectious diseases, neurological disorders, and cancer.

What is the effect of donation-induced iron deficiency on blood donor health?

Blood donation removes iron, and frequent blood donors commonly have low or absent iron stores.⁵² Donation frequency remains the strongest predictor of iron depletion among all donors, after controlling for body mass, race/ethnicity, and polymorphisms affecting iron metabolism. Less well documented is the effect of iron depletion on blood donor health and well-being. Iron deficiency may have multiple physical and neurologic consequences, including impaired work capacity, altered cognitive function, pica, and restless legs syndrome. The prevalence, duration, and severity of these conditions in blood donors are poorly elucidated. In contrast, modest iron deficits might protect against cancer and cardiovascular disease. It is feasible to connect donor information with clinical databases to study whether donation behavior and iron status have long-term consequences for donor health.

Are donor factors (e.g., age, gender), whole blood processing methods, and/or RBC storage solutions associated with in-hospital mortality and/or other measures of transfusion efficacy or harm in patients who receive RBC transfusions?

There is growing evidence that donor factors (e.g., age, race-ethnicity, and/or gender), method of blood processing, and/or RBC storage solution could affect the quality of the RBC and contribute to patient adverse events. For example, RBC rigidity and oxygen saturation vary between premenopausal women and postmenopausal women and men, suggesting that donor age and/or gender may affect RBC quality and patient outcome.⁵³ A retrospective Canadian study suggested that older blood was associated with in-hospital mortality until 2006; however, after that time the risk of in-hospital mortality increased when fresher blood was transfused.⁵⁴ This change coincided with introduction of the buffy coat preparation method, suggesting that whole blood processing methods may affect patient outcomes.⁵⁴ Recipient datasets from randomized controlled transfusion trials are available and it is feasible to link this information to blood donor and blood product information.

How can blood centers reduce injuries after blood donation?

Blood donation is generally well tolerated, but some people experience adverse reactions, such as lightheadedness or loss of consciousness.^{55,56} Injuries that result from loss of consciousness after blood donation can (rarely) cause significant morbidity or disability and are likely underreported because they often occur after the donor leaves the blood center. Further efforts should design, implement, and monitor strategies to reduce injuries after blood donation and optimize donor health. Reducing injuries will require identifying susceptible donors, providing them with post-donation care instructions, and improving their ability to recognize prodromal symptoms and respond to orthostatic changes in blood pressure. Technology for personalized medicine platforms could be developed to capture information about post-donation reactions and facilitate real-time interactions with blood

donors, enable blood centers to design and deliver intervention to prevent post-donation injuries, and optimize donor health.

Overarching Themes

In addition to the specific questions developed by the individual committees and discussed in the general sessions, several cross-cutting themes relevant to each of these four areas were identified, including the following:

1. “What's in the bag?” Identify and quantify the components of each type of blood product to improve their quality, reproducibility, and robustness..
2. “Are the current numbers we use (e.g., hematocrit, platelet count, prothrombin time (INR)) the relevant ‘transfusion triggers’?” Evaluate appropriate, pathophysiologically-relevant indications and biomarkers for transfusing individual patients in specific clinical settings.
3. “How do we know if it works?” Establish appropriate, physiologically-relevant markers to determine transfusion effectiveness. These markers may be laboratory values or other measures of clinical status.
4. “How can we make better products?” Develop improved methods for preparing classical products and determine whether there are alternative ways of preparing analogues (e.g., synthetic, bioengineered, “bio-Pharmed”).
5. “How can we better protect our donors?” Understand the physiological changes occurring in donors during and after donation.
6. More studies on transfusion therapy for pediatric patients and, separately, on neonates are urgently required.
7. Basic descriptive and observational data need to be compiled in robust databases to allow for hypothesis testing and generation, and to inform clinical trial study design
8. Basic mechanistic research, in addition to performing clinical trials, is needed.
9. It is important to educate health care providers and the lay public on important new clinical research findings to reduce the time interval to adoption
10. An improved understanding of clinical hemostasis is necessary to inform the use of transfusion products for managing hemostatic disorders. In particular, appropriate levels of circulating RBCs, platelets, and coagulation factors, and an improved understanding of their interactions, are all important factors to ensure appropriate hemostasis.
11. There is a need for enhanced training and education in transfusion medicine to facilitate and promote research in transfusion medicine, train transfusion medicine physicians, and educate physicians and nurses who prescribe and use blood components.

It is hoped that addressing these scientific priorities with careful attention to the overarching themes, will provide a solid platform for transforming the practice of transfusion medicine over the next 5-10 years.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

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The Working Group Chairs, Co-Chairs, and Members, along with the Keynote Speakers, are listed below:

RBC Working Group: Naomi L. C. Luban (Chair), Nareg H. Roubinian (Co-Chair), Jeanne Hendrickson, James C. Zimring, Karina Yazdanbakhsh, Megan Delaney, Russell E. Ware, Alan Tinnmouth, Allan Doctor, Anna Rita Migliaccio, Dean A. Fergusson, John A. (Jack) Widness, Jeffrey L. Carson, John Hess, John D. Roback, Jonathan H. Waters, Jose A. Cancelas, Mark T. Gladwin, Mary A.M. Rogers, Paul C. Hébert, Paul Ness, Sunil Rao, Timothy R. Watkins.

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Donor Issues Working Group: Dana V. Devine (Chair), Anne F. Eder (Co-Chair), Barbara J. Bryant, Joe E. Kiss, Michael P. Busch, Roger Y. Dodd, Nancy M. Heddle, Bryan R. Spencer, Anthony J. Keller, Marc Germain, Mindy Goldman, Peter A. Tomasulo, Wim de Kort, Anna van Dongen, James C. Zimring, Alan E. Mast, Richard O. Francis

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Figure 1.

Example of an adaptive trial design. Sequential increases in INR threshold are used for randomization and the design allows for information obtained in the early portion of the trial to inform the feasibility and safety of continuation.