Design of the Randomized Controlled Trial Comparing Dimethyl Sulfoxide Cryopreserved Platelets to Liquid Stored Platelets in Patients Undergoing Cardiopulmonary Bypass Surgery

Glenn Whitman, MD,a Robert Kramer, MD,b Kenichi Tanaka, MD,c John Holcomb, MD,d G. Michael Fitzpatrick, PhD,e Jacob Raphael, MD,f and Paul Ness, MDg

ABSTRACT

Objective: Dimethylsulfoxide-cryopreserved platelets are being evaluated for treatment of acute hemorrhage in patients with thrombocytopenia or platelet dysfunction when liquid stored platelets are unavailable. Patients undergoing cardiac surgery with cardiopulmonary bypass with risk factors for significant bleeding represent a population for which determining efficacy and safety of cryopreserved platelets is ideal in the clinical trial setting. The primary objective is to compare blood loss in cardiopulmonary bypass patients receiving cryopreserved platelets or liquid stored platelets.

Methods: In patients undergoing cardiac surgery utilizing cardiopulmonary bypass, a standardized algorithm with transfusion triggers will be used to guide the intra- and postoperative administration of study platelets, either cryopreserved platelets or liquid stored platelets, based on the clinical presentation. The primary efficacy endpoint was the volume of blood loss from completion of chest closure (time 0) until the time chest tubes were removed or 24 hours after chest closure, whichever is earlier.

Results: This design article describes an ongoing multicenter, randomized, blinded trial to evaluate noninferiority or superiority of cryopreserved platelets with liquid stored platelets in controlling blood loss in patients undergoing cardiopulmonary bypass surgery.

Conclusions: Frozen storage could substantially safely extend the shelf life of stored platelets. If efficacy and safety were demonstrated in this trial, current constraints on platelet use in low resource military and civilian settings would be relieved. (JTCVS Open 2022;1:1-10)

CENTRAL MESSAGE

Frozen storage could safely extend the shelf life of stored platelets significantly.

In the United States, the national blood and blood component supply had been shrinking even before the COVID-19 pandemic. The pandemic has exacerbated the problem. This shortage is not just a national problem, but also an international: There have been declines in blood collection along with a shrinking donor population. The blood supply and platelet shortage is exacerbated because significant portions of donations go out of date and are never used.
transfused. For example, in 2015, roughly 12,600,000 units of whole blood and apheresis red cells, with a shelf life of 42 days, were collected in United States, of which approximately 600,000 units expired and were never transfused, representing 5% of collected units. Because of their short shelf life of 5 to 7 days, of 2.4 million platelets distributed, 242,000 units become outdated at collection centers or hospitals before being transfused, representing 10% of collections. The short 5-day shelf life of liquid stored platelets (LSPs) also results in limited access to platelet support at remote sites. Furthermore, by the time a site receives LSPs, there are <5 days before they outdate because of time for transportation and processing.

In a hypothesis driven study, in a mass casualty event, 10 of 16 trauma centers would exhaust their supply of platelets before red cells and allow for fewer than 2 massive transfusion patients to be effectively treated as a result of insufficient platelet supplies. This shortage is problematic because, as the Pragmatic, Randomized Optimal Platelet and Plasma Ratios (PROPR) trial showed, early administration of platelets is associated with a decreased 24-hour and 30-day mortality in patients with trauma who are hemorrhaging.

Blood transfusions are a part of therapy in approximately 4% of US hospitalizations. Over the past 15 years, blood transfusions have decreased as their risks and benefits have been better understood. This recognition has led to a decrease in blood transfusions by more than 25% between 2009 and 2016. Less demand, the high cost of acquisition, and consolidations to control expenses have led to a significant reduction in the number of blood donation centers, further exacerbated by payments to collection centers from hospitals that are often lower than acquisition and preparation costs. The interplay of these forces has led to a US blood supply that is increasingly vulnerable, preventing us from having capacity to meet unpredictable supply issues.

Specific to this problem is the issue of platelets and platelet storage. Currently, the United States has among the world’s highest rates of platelet transfusions per capita. Although there has been a decrease seen in red cell transfusions, this has not been evident for platelet transfusions. The decreased availability of all blood products, the short shelf life of platelets in the face of continued high platelet utilization has made platelet availability an acute problem throughout the country. In 2015, The Association for the Advancement of Blood and Biotherapies supported an effort to provide evidence-based guidelines for more rational platelet utilization and published clinical practice guidelines for their transfusion.

The guidelines provided evidence-based recommendations and clarity regarding risk versus benefit. In patients undergoing surgery as well as trauma, despite the fact that there is less evidence, platelet transfusions appear as part of all protocols for the treatment of hemorrhagic shock and are commonly administered for postsurgical bleeding.

To address this problem, prolonging the shelf life of platelets using cryopreservation has been proposed. For purposes of this trial, patients undergoing cardiac surgery with cardiopulmonary bypass (CPB) have been chosen as they represent a patient population for which determining the efficacy and safety of cryopreserved platelets (CPPs) is ideal in the randomized controlled clinical trial setting. Thrombocytopenia and platelet dysfunction are important causes of hemostatic dysfunction following CPB. Patients undergoing cardiac surgery receive antithrombotic therapy before surgery at times and platelet function that is decreased preoperatively can be further exacerbated postoperatively by the use of CPB. Platelet transfusion therapy has been a major component in the management of bleeding after CPB. In fact, 20% to 60% of all adult patients undergoing heart surgery receive postbypass platelet transfusion. The measurement of chest tube drainage, a metric available in all cardiac surgery, can represent a surrogate for real-time platelet function.

This article will present, in a narrative form, the design of the ongoing Randomized Controlled Trial Comparing Dimethyl Sulfoxide Cryopreserved Platelets to Liquid Stored Platelets in Patients Undergoing Cardiopulmonary Bypass Surgery (CRYPTICS) trial (ClinicalTrials.gov identifier: NCT04709705), a multicenter, randomized controlled trial comparing cryopreserved platelets with liquid stored platelets in controlling blood loss in patients undergoing cardiopulmonary bypass surgery.

One might ask why we are eager to publish a design article that describes a trial well in advance of completion. Because of the enrolling and selection process in conducting this trial, and what we consider its pivotal nature, we want to raise an awareness of this trial while it is going on, especially to the cardiac surgery community. Creating awareness of this trial in the cardiac surgery community may help enrollment as the trial gathers momentum and we consider adding more sites. In addition, the time from establishing evidence (eg, publishing, Food and Drug Administration approval, production, and postmarketing...
trials) to implementation may be shortened by public knowledge of this trial.

**Trial Objectives**

The primary objective of CRYPTICS is to compare postoperative blood loss in patients undergoing CPB surgery who received CPPs and those who received LSPs. It is hypothesized that chest tube drainage (CTD) in patients receiving CPPs will be non-inferior to or significantly less than the amount in patients who received LSPs. A 2-stage analysis will test first if the CTD is noninferior between groups, and, if noninferiority is shown, the superiority of CPPs over LSPs will be tested. In addition, chest tube volume and rate, blood products and clotting factor concentrates, time to hemostasis (defined as the time from protamine administration to the time when the surgeon initiates the first suture for chest closure), and rates of surgical re-exploration will be included as secondary efficacy objectives.

**Trial Design**

This study is a randomized, blinded, parallel group trial to evaluate the noninferiority or superiority of CPP with LSP in controlling blood loss in patients undergoing CPB surgery. Patients planning to undergo CPB surgery with risk factors for significant bleeding postsurgery will be approached, have the nature of the study explained to them, and if willing, be consented per local site policy. After eligibility screening, patients will be randomized following their preoperative visit and at least 1 day before surgery. Eligible patients will undergo CPB surgery and at the completion of bypass and heparin reversal, and if warranted by the protocol algorithm, will receive platelets as per their randomization, intraoperatively, postoperatively, or both. (Figure 1).

To minimize bias with respect to selection of subjects in need of a platelet transfusion as well as the timing and dose of all blood products, transfusion triggers should follow the established guidelines or algorithms. In the case of a bleeding patient, this algorithm will guide the surgeon and/or the anesthesiologist across all study sites with respect to when intraoperative or postoperative study platelets and other blood components (ie, red blood cells, plasma, or cryoprecipitate) or biologics are administered. Figures 2 and 3 show the algorithms endorsed by the Society of Cardiovascular Anesthesiologists delineating transfusion triggers. Figure 1 is based on the standard laboratory tests including hemoglobin, platelet count, Clauss fibrinogen level, prothrombin time, activated partial thromboplastin time, and activated clotting time. Viscoelastic coagulation tests can also be utilized to guide hemostatic interventions, including thromboelastography (Haemotechnology), rotational thromboelastometry (Instrumentation Laboratory), and Quantra (HemoSonics).

If, while normalizing all coagulation defects intraoperatively as per the standard algorithm, clinically significant bleeding persists and a platelet defect is suspected, study platelets may be given. Postoperatively, the metric to assess bleeding is CTD. If the CTD rate is >200 mL/hour with the rate calculated on a minimum of 15 minutes of CTD collection, based on the standard protocol above, study platelets (1 unit of CPP or LSP per randomized treatment assignment) as well as other blood products will be given as recommended in the algorithms. If the calculated bleeding rate continues to be >200 mL/hour or > 150 mL/hour for 2 consecutive hours, and after normalizing all other coagulation defects as per the standard algorithm, patients will receive additional doses of study platelets, up to a total of 3 doses of study platelets. Both in the intraoperative and postoperative settings, if a qualitative platelet defect is suspected, while normalizing all coagulation defects according to the algorithms, study platelets may be given.

Thereafter, treatment of refractory bleeding will be standard of care for the local institution. For bleeding rates >400 mL/hour with hemodynamic instability, postoperative transfusion criteria may be non–lab-value directed and guided by the surgeon and/or anesthesiologist. If exploratory reoperation is performed, the cause of bleeding will be recorded. The primary efficacy end point is to compare the volume of blood loss from completion of chest closure (time 0) until the time chest tubes are removed or 24 hours after chest closure, whichever is earlier between patients who received cryopreserved platelets and those who received standard LSPs. The cumulative amount will be summed for the primary efficacy end point. Secondary efficacy objectives include comparing CTD volume and drainage rate at 6-hour intervals up to 24 hours, determining amount of blood products transfused, clotting factor concentrates administered, the incidence of patients who undergo re-exploration for bleeding, and time to hemostasis. Time to hemostasis is defined as the time from protamine administration to the time when the surgeon initiates the first suture for chest closure. Secondary safety objectives include assessing the safety of CPPs compared with LSPs with respect to frequency and severity of adverse events, including the incidence of thromboembolic complications, transfusion reactions, significant changes in vital signs, abnormal laboratory tests, clinically relevant electrocardiogram findings and myocardial infarction, evidence of acute renal injury, and all-cause mortality at 30 days postsurgery. Safety end points will be assessed from the start of the first study platelet transfusion until release from the hospital or at the end of study day 6, whichever is earlier. Thirty-day all-cause mortality and use of any renal replacement therapies from the end of surgery until day 30 will also be recorded.

**CPP**

The investigational product, CPP, is prepared from a pool of irradiated, Group O leukocyte reduced apheresis units that have been collected in accordance with Food and
Drug Administration and Association for the Advancement of Blood and Biotherapies requirements. Each production batch consists of up to 12 individual, irradiated, and leukocyte-reduced apheresis platelet units collected from up to 10 donors. The pooled units undergo further processing for concentration, addition of dimethyl sulfoxide (DMSO) and frozen storage at $< -65^\circ C$ to produce pooled CPP. DMSO is an organic solvent that is the cryoprotectant used in this study.

Stability data indicate the product can be stored for up to 5 years. A unit of frozen CPP contains $\geq 1.7 \times 10^{11}$ irradiated platelets and approximately 6% DMSO with residual plasma in a final frozen volume $\geq 20$ mL to $\leq 35$ mL. Thawed units of CPP are resuspended with 25 mL 0.9% sodium chloride for injection. Once resuspended, the DMSO content is reduced to approximately 3%. Thawing and resuspension requires approximately 15 minutes. The process flow diagram showing the steps for thawing and resuspension of frozen CPP is shown in Figure 4. Unlike other CPP formulations and preparations, the 30-minute rest period after thawing and reconstitution has been eliminated with no influence on product quality. For this study, to make

\begin{figure}
\centering
\includegraphics[width=\textwidth]{trial_design.png}
\caption{Trial design. CPP, Cryopreserved platelets; LSP, liquid stored platelets; ECG, electrocardiogram; CPB, cardiopulmonary bypass; ACT, activated clotting time; pRBC, packed red blood cells; CRYO, cryoprecipitate; CTD, chest tube drainage.}
\end{figure}
Cardiac Surgery Intraoperative Targeted Transfusion Algorithm

- Perform ROTEM/TEG during rewarming phase of bypass
- Optimize Temperature (> 36 deg C), pH (> 7.2), iCa++ (> 1 mmol/L), and Hb (> 7.5 g/dL)
- Continue antifibrinolytics and consider ANH, mini circuits, retrograde priming and cell salvage

<table>
<thead>
<tr>
<th>In the presence of excessive microvascular bleeding</th>
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<tbody>
<tr>
<td><strong>ROTEM delta</strong></td>
</tr>
<tr>
<td>Rule out residual Heparin</td>
</tr>
<tr>
<td>INTEM CT &gt; 240 s ** AND ** HEPTEM CT/INTEM CT &lt; 0.9</td>
</tr>
<tr>
<td>Protamine</td>
</tr>
<tr>
<td>TEG R &gt; hTEG R x 1.25</td>
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<tr>
<td><strong>TEG 5000</strong></td>
</tr>
<tr>
<td><strong>FIBTEM A10 &gt; 10 mm ** AND ** EXTEM A10 &lt; 40 mm</strong></td>
</tr>
<tr>
<td>Platelets ± DDAVP 0.3 mcg/kg</td>
</tr>
<tr>
<td>MA &lt; 40 mm ** AND ** FF &gt; 8 mm</td>
</tr>
<tr>
<td><strong>Restore Platelets</strong></td>
</tr>
<tr>
<td><strong>FIBTEM A10 &lt; 10 mm ** AND ** EXTEM A10 &lt; 40 mm</strong></td>
</tr>
<tr>
<td>Cryoprecipitate OR Fibrinogen concentrate*</td>
</tr>
<tr>
<td>MA &lt; 40 mm ** AND ** FF &lt; 8 mm</td>
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<tr>
<td><strong>Restore Fibrinogen</strong></td>
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<tr>
<td>EXTEM CT &gt; 100 s</td>
</tr>
<tr>
<td>** Replace Factors**</td>
</tr>
<tr>
<td>INTEM or EXTEM ML &gt; 7% @ 30 min ** OR ** ML &gt; 15% @ 60 min</td>
</tr>
<tr>
<td>Aminocaproic Acid OR Tranexamic Acid</td>
</tr>
<tr>
<td><strong>Address Fibrinolysis</strong></td>
</tr>
<tr>
<td><strong>LY30 &gt; 7.5%</strong></td>
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</tbody>
</table>

Recheck ROTEM/TEG after each round of analysis
If bleeding persists despite normal ROTEM/TEG- consider surgical re-exploration.
PCCs are NOT recommended if ECMO or HIT are present
* Where available and approved for use
** “Low dose” PCC recommended but exact dosage has not been defined.

FIGURE 2. Viscoelastography algorithm. ROTEM, Rotational thromboelastometry; TEG, thromboelastography; iCa++, ionized calcium; Hb, hemoglobin; ANH, acute normovolemic hemodilution; INTEM, intrinsic pathway thromboelastometry; CT, clotting time; HEPTEM, heparinase thromboelastometry; R, reaction time; hTEG, heparinase thromboelastography; FIBTEM, fibrinogen based thromboelastometry; A10, amplitude at 10 minutes; EXTEM, extrinsic pathway thromboelastometry; DDAVP, 1-deamino-8-D-arginine vasopressin; MA, maximum amplitude; FF, functional fibrinogen; FFP, fresh frozen plasma; PCC, prothrombin complex concentrate; ML, maximum lysis; LY30, clot lysis at 30 minutes. Reprinted with permission from reference 13. *Where available and approved for use. ** Low-dose PCC recommended but exact dose has not been defined.

the transport time the same from the time of ordering LSP or CPP, for those patients randomized to CPP, 1 dose of CPP will be thawed and ready to deliver before CPB cessation. Postthaw stability has been established at 8 hours.

**Patient Population**

The patient population includes adult patients undergoing CPB surgery with at least 1 risk factor for significant bleeding postsurgery, including all reoperative cardiac
procedures, expected bypass >120 minutes, any combined cardiac surgery procedures (eg, multiple valve or valve/coronary bypass grafting) or any intrathoracic procedure (with CPB) confined to the chest. Exclusion criteria include isolated CPB surgery, ventricular assist devices, heart transplantation, thoracoabdominal aneurysm repair, as well as other patient-specific factors. After signing the informed consent, eligibility will be confirmed, and patients will be randomized before initiation of the surgical procedure 1:1 to receive either CPP or LSP (Figure 5). The intent-to-treat population includes all patients randomized to study treatment.

Because not all randomized patients will bleed excessively and not all those who bleed may require platelets, there is a modified intent-to-treat (mITT) population that includes all randomized patients who received at least 1 study platelet transfusion. This mITT population will be the primary analysis population for efficacy. The safety subset includes all patients who were randomized and received a study platelet transfusion and will be analyzed as they were treated.

Although the path to receiving platelets seems convoluted, the challenge in enrollment is to find patients who are more likely to bleed after cardiac surgery and in that subset find patients who bleed excessively and qualify for platelet transfusions for reasons of quality or quantity. The inclusion and exclusion criteria create a narrow corridor of patients more likely than average to bleed postoperatively. Most of those patients do not bleed excessively.
Of the ones who do bleed, not all of them will require platelets. For each patient who is transfused with CPP or LSP, many more must be prescreened, screened, consented, and randomized.

**Sample Size and Statistics**

As outlined in an idealized consolidated standards of reporting trials diagram in Figure 6, a sample size of 200 total patients (approximately 100 in each group) meeting the criteria for the mITT population was based on previous literature. A single interim analysis of the mITT patients is planned after 150 patients are treated (75 in each treatment arm) to assess whether or not to stop for overwhelming efficacy or futility, or to determine if an increase in sample size from 200 is warranted. Overwhelming efficacy is defined as showing at least noninferiority of CPP to LSP. Descriptive statistics will be used to present the study data. Discrete variables will be presented as number of observations and percentages. Continuous variables will be given as mean ± SD or median and range. Efficacy end points for continuous data will be evaluated for normality and transformed if there is substantial departure from normality. All data will be presented in either a listing, summary table, or both. For summary descriptive statistics, missing data will be represented by counts, will be treated as missing at random, and no adjustments will be made. Analyses of efficacy end points will be performed for the mITT population. All statistical analyses will be performed using SAS (SAS Institute Inc).

A 2-stage analysis will be used to analyze the primary efficacy end point (total CTD) in the mITT population. Non-inferiority will be tested first, and then superiority will be tested if noninferiority is shown. CTD volumes and other continuous end points will be evaluated for normality in distribution; if they are not normally distributed, then an appropriate transformation will be performed. The least squares mean ± SD, and 95% CI will be obtained from an analysis of covariance (analysis of covariance model) with treatment and clinical site, as covariates.

The difference between the least squares mean total CTD volume for patients receiving LSP compared with those receiving CPP will be analyzed with a 95% CI. This study is designed with at least 90% statistical power for the upper limit, 97.5%, of the 95% CI around the mean difference in total CTD volume (least squares mean CPP—least squares mean LSP) to exclude 400 mL. If the upper limit does exclude 400 mL, then CPP will be considered noninferior.

If the study meets the criteria for noninferiority and least squares mean CPP total CTD volume is less than the least squares mean LSP, then superiority will be tested. Specifically, an analysis of covariance model with treatment and clinical site as covariates will be used to compare the least squares means between groups. Multiple imputation will be used to account for missing data in the primary analyses.

**DISCUSSION**

Along with dissemination of evidence-based indications for platelet utilization, a review by Stubbs and colleagues described 4 approaches. The first was to economically incentivize the donor population. The second was to decrease the minimum required content for an apheresis platelet unit from $\geq 3 \times 10^{11}$ platelets. The third, addressed the issue of storing platelets at 1 to 6°C, rather than at room temperature. These cold storage platelets, which have been shown to be successfully stored for 14 days, would immediately increase platelet supply. Although they do not last as long in circulation and are thus not indicated for prophylaxis for thrombocytopenia, these platelets are more hemostatic than room temperature platelets and currently are approved by the US Army and US Air Force. The fourth approach describes platelet cryopreservation (ie, CPPs) that would extend the shelf life of stored platelets to years as opposed to days. In addition to prolonging the storage time of platelets addressing the issue of availability, there is some evidence that CPPs have enhanced hemostatic capability due to activation in the storage and reconstitution process. Based on a small, randomized trial as well as retrospective data, the Dutch military utilized DMSO CPPs in Iraq and Afghanistan from 2001 to 2012. In a retrospective review of their
experience, treatment of trauma cases with a higher ratio of frozen platelets to other blood products (packed red blood cells and fresh frozen plasma) resulted in increased survival rates.\textsuperscript{28-30}

In the target population for this proposed study, we are aware that CPB induces complex hemostatic defects that lead to increased blood loss that has been associated with up to an 8-fold increase in the odds of death (95\% CI, 3.9-17.0).\textsuperscript{8,11,31,32} Platelet transfusion therapy has been a major component in the management of bleeding after CPB as the CPB-induced hemostatic dysfunction is related in part to platelet dysfunction.\textsuperscript{7,8}

In 1992, in a randomized controlled trial of patients with bleeding after CPB surgery, DMSO CPPs were compared

\begin{figure}
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\includegraphics[width=\textwidth]{figure5}
\caption{Inclusion and exclusion criteria. CABG, Coronary artery bypass grafting; DMSO, dimethyl sulfoxide.}
\end{figure}

\begin{figure}
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\includegraphics[width=\textwidth]{figure6}
\caption{Consolidated standards of reporting trials diagram. mITT, Modified intention to treat.}
\end{figure}
with LSP for management of postoperative hemorrhage in a small study. In that study, patients were assigned to receive CPPs (24 patients) or standard LSPs (29 patients). Nonsurgical blood loss was measured during and after the operation as the primary outcome measure. The median total blood loss in the patients receiving the CPP transfusions was significantly less than those receiving the LSP transfusions. That study used a different method to prepare CPP than the method proposed in CRYPTICS. The cryopreservation process in that trial involved freezing platelets with 6% DMSO at $-65^\circ$C, thawing, washing (removing DMSO), and resuspending them in plasma, whereas the method used in CRYPTICS eliminates the postthaw wash step as the amount of DMSO in the product is clinically not significant. A Phase I study has been successfully completed using this freezing and thawing method in 28 patients with thrombocytopenia with refractory bleeding despite having received LSP.33

The Cryopreserved vs. Liquid Platelets (CLIP)-I trial, a recent (2019) pilot randomized controlled trial in cardiac surgery patients, found that compared with LSPs, CPPs were associated with no evidence of harm.29 Editorial comments regarding CLIP-I emphasized the value of CPPs being useful for patients undergoing procedures with expected platelet use, such as CPB.34 CLIP II, The Cryopreserved versus Liquid Platelets Trial (ClinicalTrials.gov identifier: NCT03991481), sponsored by the Australian and New Zealand Intensive Care Research Center, is currently enrolling high-risk cardiac surgery patients in Australia. It is a Phase 3 multicenter, blinded, randomized controlled clinical non-inferiority trial examining CPP versus LSP for the management of surgical bleeding. Since 1972, more than 3000 CPP transfusions have been given in various trials to 1334 patients.35 All of these studies support the safety and efficacy of platelets cryopreserved in DMSO.

DMSO platelet cryopreservation would be a significant development in addressing the worldwide shortage of platelets. Patients undergoing cardiac surgery represent an ideal population to determine their efficacy and safety in a randomized controlled clinical trial setting. CRYPTICS represents the latest and most definitive clinical trial in the United States testing the use of platelets cryopreserved in DMSO.

CONCLUSIONS
CRYPTICS will examine the clinical effectiveness and safety of a DMSO-based method of platelet cryopreservation in patients undergoing cardiac surgery who meet criteria for platelet therapy due to postoperative bleeding. A result of noninferiority could pave the way to relieve platelet shortages throughout the world, especially in low-resource and austere environments. In addition to easing inventory problems in high-volume urban centers, it would allow rural and far-forward military settings to have a safe, effective platelet product with a long shelf life in their blood bank inventory.

Conflict of Interest Statement
Dr Whitman receives a consulting fee for working with Avania as a member of its executive board for this project. Dr Holcomb is a consultant with Cellphere, Thornhill Medical, and Arsenal; is co-founder, co-CEO, and on the Board of Directors of Decisio Health; is on the Board of Directors of QinFlow, Zibrio, Hemostatics, CCI Medical, and Oxygen; and is a coinventor of the Junctional Emergency Tourniquet Tool. Dr Fitzpatrick is a full-time employee of Cellphere Therapeutics. Dr Raphael is on the advisory board of Octapharma USA. All other authors reported no conflicts of interest.

The Journal policy requires editors and reviewers to disclose conflicts of interest and to decline handling or reviewing manuscripts for which they have a conflict of interest. The editors and reviewers of this article have no conflicts of interest.

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**Key Words:** cryopreserved platelets, bleeding, blood coagulation, cardiopulmonary bypass, clinical trials