The design of an adaptive clinical trial to evaluate the efficacy of platelets stored at low temperature in surgical patients

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BACKGROUND: Storage of platelets at 4°C compared with 22°C may increase both hemostatic activity and storage duration; however, the maximum duration of cold storage is unknown. We report the design of an innovative, prospective, randomized, Bayesian adaptive, "duration finding" clinical trial to evaluate the efficacy and maximum duration of storage of platelets at 4°C.

METHODS: Patients undergoing cardiac surgery and requiring platelet transfusions will be enrolled. Patients will be randomized to receive platelets stored at 22°C up to 5 days or platelets stored at 4°C up to 5 days, 10 days, or 15 days. Longer durations of cold storage will only be used if shorter durations at 4°C appear noninferior to standard storage, based on a four-level clinical hemostatic efficacy score with a NIM of a half level. A Bayesian linear model is used to estimate the hemostatic efficacy of platelet transfusions based on the actual duration of storage at 4°C.

RESULTS: The type I error rate, if platelets stored at 4°C are inferior, is 0.0247 with an 82% probability of early stopping for futility. With a maximum sample size of 1,500, the adaptive trial design has a power of over 90% to detect noninferiority and a high probability of correctly identifying the maximum duration of storage at 4°C that is noninferior to 22°C.

CONCLUSION: An adaptive, duration-finding trial design will generate Level I evidence and allow the determination of the maximum duration platelet storage at 4°C that is noninferior to standard storage at 22°C, with respect to hemostatic efficacy. The adaptive trial design helps to ensure that longer cold storage durations are only explored once substantial supportive data are available for the shorter duration(s) and that the trial stops early if continuation is likely to be futile. (*J Trauma Acute Care Surg.* 2018;84: S41–S46. Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.)

KEY WORDS: Adaptive trial design; Bayesian statistics; platelet transfusion; hemostatic agents; blood banking.

Annually, there are over 5 million trauma-related deaths worldwide, accounting for nearly 10% of all fatalities. Unintentional injury-related deaths in children are estimated to be 730,000 annually worldwide. In the United States, trauma is the third overall leading cause of death for all ages and the leading cause of death for those 1 year to 46 years of age. Trauma is also the most common cause of life-years lost before the age of 75 years.[1] Preventable deaths after traumatic injury have been defined as "casualties whose lives could have been saved by appropriate and timely medical care, regardless of tactical, logistical, or environmental issues."[1] In the United States, each year, there are an estimated 30,000 preventable deaths after injury due to posttraumatic hemorrhage.[2] If the US data are generalizable to the global incidence of trauma-related deaths, there are approximately 1 million preventable, trauma-related deaths per year due to severe bleeding. These preventable death statistics do not include other etiologies of life-threatening hemorrhage. The benefits gained by improving resuscitative practice for trauma patients will very likely also improve outcomes for patients with life-threatening bleeding due to nontraumatic causes.

Damage Control Resuscitation (DCR) practices have been developed to reduce death from hemorrhagic shock.[3,4] The DCR principles have been generalized to many nontrauma populations with life-threatening bleeding, such as obstetric,[5] gastrointestinal,[6] and operative patients.[7] Perioperative bleeding in cardiac surgery can be significant and is associated with poor outcomes.[8–13] A central tenant of DCR is hemostatic resuscitation, which aims to use whole blood or its equivalent in components to provide a balanced approach to simultaneously address both oxygen debt and hemostatic dysfunction. Platelet transfusions are a key component of this strategy; however, platelet availability is hampered by the relatively brief maximum duration of storage that is safe at 22°C.

To address this challenge in patient with life-threatening hemorrhage, there is interest in reevaluating the storage of platelets at 4°C, compared with 22°C, since both in vitro and clinical trial data indicate that cold storage temperature improves the hemostatic function of platelets and reduces bacterial contamination.[2,14–20] Storage at 4°C could also improve the availability of platelets, if the maximum duration of cold storage is found to be substantially longer (e.g., up to 15 days) than the 5-day maximum duration of storage at 22°C. This would dramatically increase availability of platelets in hospitals that cannot keep platelets in inventory due to the current shelf life of 5 days.

To determine the efficacy and safety of 4°C versus 22°C storage of platelets in cardiac surgery patients with severe bleeding

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requiring platelet transfusion, we plan to conduct a randomized clinical trial that will incorporate adaptive trial design methodology to efficiently identify the longest duration of storage of platelets at 4°C that results in clinical efficacy that is noninferior to storage at 22°C and determine whether platelets stored at 4°C are superior in hemostatic efficacy. An adaptive trial design—namely, a trial in which changes may be made to key clinical trial characteristics (e.g., the maximum duration of storage at 4°C) in response to incoming data, according to prespecified rules—may be able to achieve greater statistical efficiency than a fixed trial design.[21,22] The data generated in this trial with cardiac surgery patients may be generalizable to other patient populations with life-threatening hemorrhage to include traumatic injury, and gastrointestinal and obstetric bleeding. Here, we present rationale for the planned trial design, the current trial design itself, and its performance and operating characteristics.

METHODS: CLINICAL TRIAL DESIGN STRATEGY

Trial Goals

The goal of the trial is to determine whether platelets stored at 4°C are noninferior (or superior) in terms of hemostatic efficacy relative to platelets stored at 22°C and, if so, to determine the maximum duration of storage at 4°C that maintains noninferiority.

Challenges Facing a Traditional Clinical Trial Design

A number of challenges would face researchers intending to use a traditional, nonadaptive trial design to address the trial goals above. First, if the trial was conducted with a fixed maximum duration of cold storage that was smaller than the true maximum duration of effective cold storage, then we would fail to demonstrate the full potential for longer durations of storage at 4°C. Alternatively, if the trial was conducted with a fixed maximum duration of cold storage that was longer than the true duration of cold storage that maintains noninferiority, then the mixture of longer-stored inferior and shorter-stored noninferior platelets in the experimental arm could decrease the power of the trial, expose patients to excessive risk, and lead to a failure in identifying the true maximum noninferior duration of cold storage. Finally, if the trial were conducted using fixed randomization between warm storage and all three possible durations of cold storage—a four-arm trial—then substantial patient resources might be allocated to durations of storage that were ultimately of little interest or were found to be inferior, leading to statistical inefficiency or an increase in risk to study participants.

Process of Adaptive Trial Design

The process by which an adaptive clinical trial is designed is different than for a more traditional trial. The goal of an adaptive trial is to respond to incoming information during the trial, by changing key components of the trial design according to prespecified rules, in a manner that increases the probability of trial success or avoids the continuation of a trial that is futile. To identify the types of adaptations that are more likely to increase the chance of success, the investigator team of clinical, blood banking, and statistical experts participated in a collaborative and iterative process. This involved considering possibilities for clinical trial design structure, Monte Carlo computer simulation of potential designs with comparisons of performance (e.g., type I error rate, power, required sample size, accuracy in determining the maximum noninferior duration of cold storage), and selection of promising designs or proposing design modifications and further simulation. This iterative process continued until the current design was defined and simulated under a variety of assumptions regarding platelet efficacy, characteristics of the enrolled patient population, and so on. The purpose of Monte Carlo simulation is not to predict the outcome of the actual trial, because that is dependent on the unknown true efficacy of cold-stored platelets of various ages, but to demonstrate good statistical performance over a wide range of possibilities for the true hemostatic efficacy of platelets stored for various durations at 4°C. The overarching goal is to design a trial that performs well, with acceptable error rates and high power, is statistically efficient, and to reduce the likelihood of continuing when futile or exposing subjects to avoidable risk.

The primary adaptive feature of the proposed trial is the variable duration of maximum platelet storage at 4°C in the experimental arm, as this was the experimental parameter that was the most uncertain based on prior work. Thus, selecting a fixed duration would have entailed greater risk of either a failed trial if the duration was too long, leading to a heterogeneous treatment effect, or a missed opportunity if the interval was too short and we failed to identify the full duration of feasible storage of platelets at 4°C.

RESULTS: THE ADAPTIVE CLINICAL TRIAL DESIGN

Patient Population

To investigate the efficacy and safety of platelets stored at 4°C efficiently, a population of patients with a predictable need for platelet transfusion and augmented hemostasis is necessary. The clinical trial will be conducted in adult and pediatric patients undergoing cardiac surgery. To be eligible for the study, the surgical procedure must use cardiopulmonary bypass and entail a high risk for platelet transfusion. Patients on antiplatelet therapies will be included. Exclusion criteria include contentious objection or unwillingness to receive blood products, transfusion of platelets or whole blood within 12 hours of the randomization, a requirement for special platelet products (e.g., HLA-matched or cross matched platelets), antibodies to platelets (e.g., anti–HPA-1a), congenital platelet disorder, IgA deficiency, pregnancy, unavailability of the platelet supply for both arms of the study, and anticipation of the need for massive transfusion.

In cardiac surgery, the incidence of intraoperative and postoperative platelet transfusion ranges between 10% and 60%, with the incidence of platelet transfusion depending on the duration and severity of surgery as well as the preoperative use of antiplatelet agents.[23–27] Cardiopulmonary bypass also causes platelet dysfunction and may increase the need for platelet transfusions postoperatively. Transfusion of 4°C platelets may provide an effective treatment for increasing platelet function and reducing bleeding in patients undergoing cardiac surgery.

Treatment Arms

The control treatment is the administration of platelets stored for up to 5 days at 22°C. The experimental arm is the

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administration of platelets stored at 4°C for up to 5 days, 10 days, or 15 days.

Outcome Measures

The primary outcome for the trial will be the hemostatic efficacy of the platelet transfusion, as assessed by a four-level or five-level global hemostatic efficacy score (HES). We illustrate the design using a four-level scale; however, extension of the design to a five-level scale is straightforward. We assume a higher numerical score signifies less bleeding, that is, higher hemostatic efficacy. The HES will incorporate both quantitative measures of bleeding (e.g., chest tube output) and subjective assessments of hemostatic efficacy based on clinicians' experience with similar patients. The four levels will be denoted as "poor," "fair," "good," and "excellent" and the noninferiority margin (NIM) will be defined as a half level within the four-level HES. The precise definition of the HES will be included in the detailed clinical trial protocol.

Overall Statistical Design

The trial design is a prospective, randomized adaptive "duration finding" trial, using a strategy that is analogous to a dose-escalation strategy that might be used in a trial of a drug. The trial begins by randomizing patients between a control arm of platelets stored for up to 5 days at 22°C ("warm") and an experimental arm of platelets stored at 4°C ("cold") also for up to 5 days. If the 4°C/5 days arm meets criteria defined below for noninferiority (or superiority) relative to warm storage, then platelets stored for up to 10 days at 4°C will be used for the experimental arm. Similarly, if the 4°C/10 days arm meets criteria for noninferiority (or superiority) relative to warm storage, then platelets stored for up to 15 days at 4°C will be used for the experimental arm. Interim analyses,[28] at which the trial may potentially change the currently enrolling duration of cold storage, are conducted every 300 subjects, beginning with the 300th patient. At each interim analysis, the maximal cold duration can be increased, remain the same, or decrease, with the goal of identifying the region of cold durations, if any, where the hemostatic efficacy of platelets stored at 4°C is noninferior to warm platelets.

Between interim analyses, the randomization ratio between the warm control arm and the currently enrolling cold storage arm is held constant; however, that ratio may change at each interim analysis. For the purposes of illustration, we have presented the simplest case in which the randomization ratio is always 1:1. Additional power may be obtained by increasing the ratio to 1:2 or 1:3 later in the trial to make the number of patients enrolled in the control arm and the longest-enrolled cold storage arm more similar at the end of the trial.

When using cold platelets of a particular maximal duration of storage, the platelets used may be of any cold duration at or below the maximal duration. When using a maximal duration of 10 days, for example, the actual platelets administered may tend to have durations between 6 days and 10 days. To obtain an accurate estimate of the mean bleeding score as it relates to duration of storage, we fit a linear regression model relating the actual duration of cold storage (X) to the mean bleeding score for that specific duration (B_X). Decisions to increase the maximum duration of cold storage are based on the model estimate of the mean bleeding score at the current maximal duration. Thus, to increase from a maximal duration of 10 days, the fitted model based on the data must indicate that exactly 10 days of cold storage results in an acceptable (noninferior) bleeding score.

Specifically, trial decisions are based an assessment of the probability of noninferiority for each cold platelet duration (X = 5, 10 or 15 days; the upper limit of storage duration in each potential experimental arm) relative to warm platelets. The NIM is a half level of the four-level hemostatic efficacy score (HES). Let B_X be the mean bleeding score for cold platelets at exactly X days cold, and B_W be the mean bleeding score for warm platelets. At each interim analysis, we compute the probability that X-day-old cold platelets are noninferior to warm platelets, denoted Pr(NI), at each duration

$$\Pr(\mathrm{NI}) = \Pr(B_X > B_W - \mathrm{NIM}),\ X = 5, 10, 15 \text{ days}$$

where the NIM of 0.5 is subtracted from the estimate of the mean bleeding score in the warm control arm, since lower hemostatic efficacy scores signify more significant hemorrhage.

To determine the maximal duration for the subjects enrolled until the next interim analyses (the next 300 patients), we use the following rules that are similar in spirit to a continual reassessment method-based dose escalation design.[29]

1. Criterion 1. If the highest maximal duration that has been used in the trial has Pr(NI) greater than 0.8, then the trial will escalate to use the next highest maximal duration, moving from 5 to 10 or 10 to 15. No escalation beyond a 15-day maximal duration of cold storage is possible.
2. Criterion 2. If escalation is not possible, either because the Pr (NI) greater than 0.8 condition is not met or the trial is already using the 15-day duration of cold storage, then the trial identifies the maximum duration of cold storage with both Pr(NI) greater than 0.60 and a sample size greater than 0. This duration of cold storage then becomes the new maximum enrolling duration of cold storage in the experimental arm. For this criterion, we do not consider durations that have not yet been explored, only criterion 1 allows escalation to a new dose.
3. Criterion 3. If no durations of cold storage satisfy the criterion that Pr(NI) greater than 0.60, the trial will stop for futility.

Criterion 1 governs the escalation to new durations, requiring a high chance of noninferiority at the maximal duration explored to date in the trial and thus a high likelihood that noninferiority will continue in the region toward the next higher duration. Criterion 2 allows the trial to move among previously explored durations, attempting to identify the highest duration continuing to demonstrate noninferiority. Criterion 3 will stop the trial if no durations are sufficiently promising.

This process will continue until all 1,500 patients are enrolled, at which point a final analysis will be conducted. The trial will be deemed successful if there is a very high final probability of noninferiority for 5 days, 10 days, or 15 days cold duration, specifically, the trial is successful if

$$\Pr(\mathrm{NI}) \geq 0.982$$

for one or more durations of cold storage.

The threshold of 0.982 has been calibrated through Monte Carlo simulation to maintain 2.5% one-sided type I error rate under the assumption that all doses are at or below the NIM. If noninferiority is demonstrated, then Bayesian posterior probabilities

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evaluating hemostatic superiority for each duration of cold storage relative to warm storage can be determined without inflation of type I error rates, as the noninferiority test is being used for gatekeeping.[30]

In assessing the performance of the design, a variety of scenarios reflecting possible underlying truths was considered. For example, all cold durations might be inferior, in which case, it is preferable that the trial declares futility as early as possible to avoid exposing patients to an inferior treatment. If all cold durations perform equivalently to warm platelets, then the goal would be to declare success with high probability while identifying that up to 15-day cold duration is noninferior to warm. If 5-day and 10-day cold platelets are noninferior but 15-day cold platelets are inferior, then the goal is to declare a successful trial while concluding that only 5-day and 10-day cold durations are noninferior to warm.

Three example scenarios used to evaluate the performance of the trial design are shown below. Scenario A is a null scenario, indicating all doses are at the NIM. Scenario B is a good scenario, where increasing durations of cold lose some effectiveness, but all durations are well within the NIM. Scenario C is a difficult situation, where 5-day and 10-day durations performing adequately but the 15-day duration is inferior. The scenarios are shown in the top row of Figure 1.

Operating Characteristics

For each of the scenarios, 10,000 virtual trials were simulated,[21] using virtual patient data generated according to the specific scenario. For the null scenario, the number of simulated trials was increased to 100,000 to more accurately identify the success threshold that maintains 0.025 type I error. The entire trial is simulated, going through each interim and following the rules based on the simulated data. Thus, each simulated trial is a possible simulated path through the trial, and their aggregate is an estimate of the probability of each outcome of interest. For

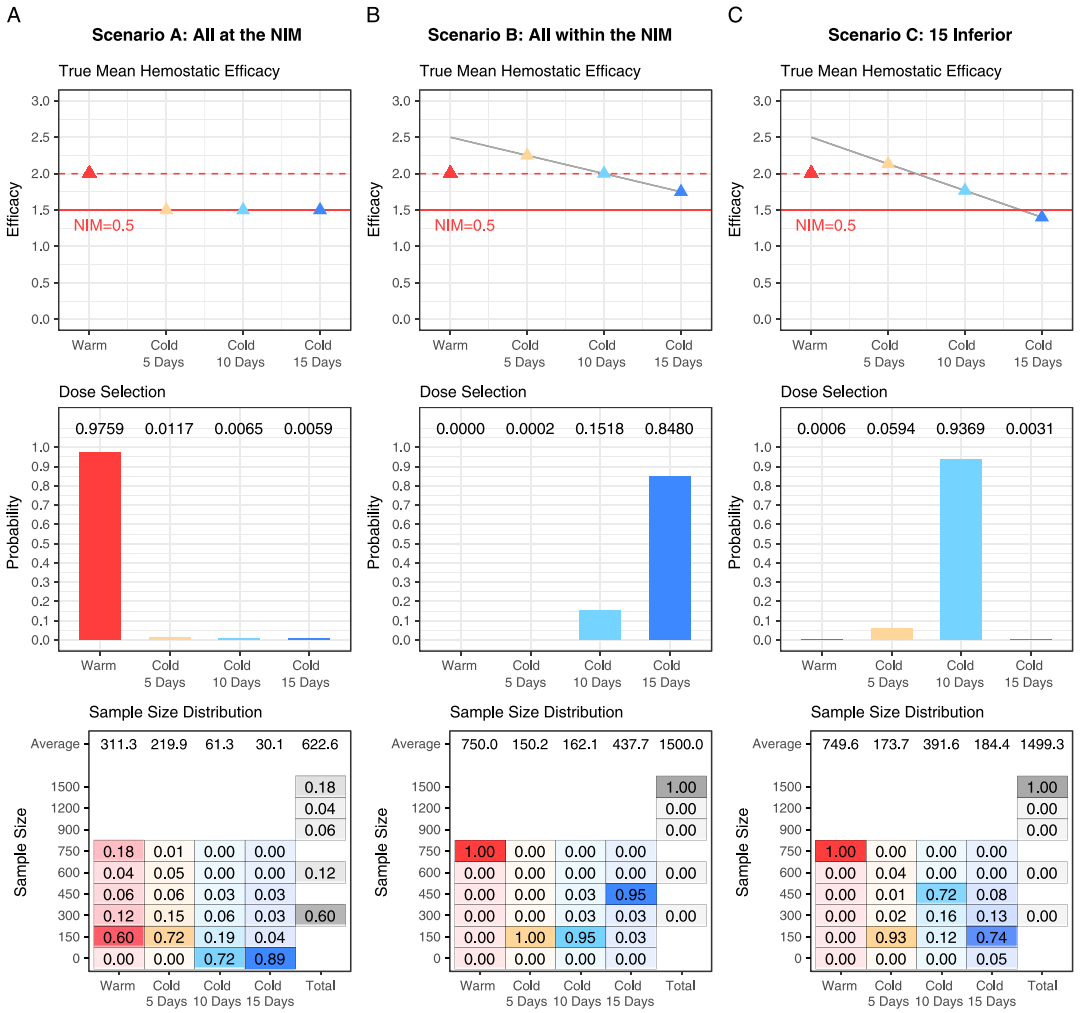

Figure 1. For each simulated scenario (scenarios A, B, and C), each row describes (1) the true mean hemostatic efficacy across all platelet storage options, (2) simulation results for dose selection describing the probability of being the maximum noninferior cold storage duration, and (3) simulation results for sample size distribution describing for each platelet storage option (and trial overall) the probability associated with enrolling each potential discrete total sample size by the end of the trial. Color represents platelet storage method; red describes warm storage while yellow, light blue, and dark blue describe up to 5 days, 10 days, and 15 days cold storage, respectively.

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example, the proportion of simulated trials that stop for futility is an estimate of the probability that, in the actual trial, the trial will stop for futility in that particular scenario.

For each scenario, we computed the probability of futility, the probability of selecting each cold duration, and the sample sizes for each of the cold durations. Figure 1 displays the results of these simulations.

In scenario A, all cold durations are at the NIM. This is a null scenario and the probability of incorrectly identifying at least one cold duration as noninferior to warm is 0.0247, maintaining a type I error rate below 2.5%. The average required sample size is 622.6 subjects. There is an 82% probability of stopping for futility prior to enrolling the full 1,500 subjects, and a 60% probability of stopping at the first interim with 300 subjects enrolled.

Scenario B illustrates a situation in which all cold durations are well within the NIM. The design always detects that cold storage is noninferior to warm storage. The probability of correctly identifying 15-day cold noninferior to warm is 0.848. As evidenced by a high probability (95%) of enrolling 450 subjects to 15-day cold storage, the design tends to increase quickly from 5-day to 10-day to 15-day cold storage and remain at 15-day cold storage for the remainder of the trial.

In scenario C, 5 days and 10 days of cold storage are noninferior to warm storage, while 15 days of cold storage is just below the NIM. The design correctly detects 10 days of cold storage as noninferior with high probability (93.7%), while incorrectly declaring 15 days of cold storage as noninferior with very low probability (0.31%). The design tends to explore all three durations of cold storage, but enrolls most heavily in an experimental arm that allows up to 10 days of cold storage.

The results indicate the design is efficient at determining whether some duration of cold storage is noninferior to warm storage, and at identifying the correct maximal duration of cold storage. The design effectively enrolls more subjects to the highest cold storage durations that appear noninferior to warm storage. If initial data suggest that one or multiple durations of cold storage are noninferior to warm storage, the design recognizes this and avoids enrolling additional subjects to those ineffective cold platelet storage durations.

DISCUSSION

Identifying a storage condition that would allow a longer maximum period of storage for platelets, while either achieving noninferior hemostatic activity or hemostatic superiority, is a critical step in increasing the supply and availability of platelets for use in treating life-threatening bleeding irrespective of the etiology. Platelet function is essential for hemostasis; therefore, the transfusion of a platelet product with maximal hemostatic potential may reduce mortality and morbidity from hemorrhage. Platelets stored at 4°C may also be safer since there is reduced risk of bacterial contamination. Standard storage of platelets at room temperature allows for potential growth of bacteria in the unit. Bacterial contamination is the highest transfusion transmitted infection risk. The prevalence of bacterial contamination of platelet components is estimated to be approximately 1:1,000 platelet components (1:994–4,739 based on initial unit cultures and 1:460–1,509 based on surveillance cultures of expired units).[31] Bacteria are less likely to grow at the colder temperature.

The proposed trial design uses a prespecified, adaptive, duration-finding strategy to efficiently and rigorously identify the maximum duration of cold storage for platelets that is noninferior to traditional warm storage with respect to overall hemostatic efficacy. The trial design possesses excellent operating characteristics, such as protection from type I error and power, while minimizing risks to subjects from being randomized to a duration of cold storage that results in inferior platelet function, or being enrolled in a trial that is unlikely to be successful and is therefore futile and unethical to continue. The trial design was developed through a strong scientific collaboration between clinical and statistical experts, using an iterative design-evaluate process informed by Monte Carlos simulation of proposed trial designs. This approach, whether applied to innovative or more traditional clinical trial designs, allows a design team to balance desired trial performance against logistical or resource limitations, and consider tradeoffs between multiple competing trial goals.

CONCLUSION

We have presented the statistical design of an adaptive clinical trial intended to determine the maximal duration of platelet storage at 4°C that results in hemostatic efficacy clinically similar or superior to storage at 22°C for up to 5 days.

AUTHORSHIP

All authors contributed to the development of the proposed trial design, writing of the manuscript, and revision for intellectual content. L.K., K.V., and R.J.L. developed the statistical design of the trial based on input from all authors. All authors take responsibility for the entire article.

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