Received: 4 February 2022 | Revised: 29 April 2022 | Accepted: 4 May 2022

DOI: 10.1111/trf.16957

TRANSFUSION

An adaptive platform trial for evaluating treatments in patients with life-threatening hemorrhage from traumatic injuries: Rationale and proposal

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KEYWORDS: adaptive trials, clinical trial design, exception from informed consent, hemorrhagic shock, medical ethics, platform trials, trauma resuscitation

1 | INTRODUCTION

Post-traumatic hemorrhage remains the leading cause of death in people aged one to forty-four in the United States.[1] The initial management of the severely injured patient, whether in the prehospital, emergency department, operating room, or critical care setting is inherently complex, with diagnostic and therapeutic strategies occurring both simultaneously and sequentially.[2,3] While substantial advancements have been made in determining optimal resuscitation in both civilian and military settings, the nature of trauma with its diverse mechanisms of injury, heterogeneous patient population, and variable access to resources makes it a challenging field in which to perform randomized controlled trials (RCTs). The paucity of high-quality randomized evidence has resulted in wide practice variation, with disparate resuscitative approaches at different medical centers and in different practice environments, which is potentially harmful to patients.[4] This is particularly true in the prehospital and early resuscitative phases of care, during which most preventable post-injury deaths occur.[5,6]

Traditional RCTs generally include two comparison groups, created by assigning members of a homogeneous patient population with equal probability to either the experimental treatment or the existing standard of care. Such RCTs are optimally structured to maximize internal

validity in the estimation of the average treatment effect of the proposed intervention in a specific patient population.[7] While traditional RCTs are the prevailing tool for generating the quality of evidence necessary to improve clinical practice, they are sub-optimal for addressing the challenge of evaluating acute and emergent therapies for life-threatening hemorrhage. Assessing the multiple therapies used in the treatment of critically injured patients via traditional RCTs would require a sequence of trials, each testing a single or few treatment arms in a restricted population. This would require many years and currently unavailable levels of funding to make meaningful progress. Further, these trials are often faced with financial and recruitment barriers that limit the rate of recruitment or the final sample size. Consequently, much of the current evidence base for the clinical care of the severely injured trauma patient comes from retrospective database analyses or animal studies, which limits its quality, scope, validity, and generalizability.[8]

Two advances in clinical research design have demonstrated substantial promise for addressing these challenges: adaptive clinical trial design[9–12] and the extension of adaptive trial methodology to platform trials.[13–17] In contrast to a traditional fixed clinical trial design in which the overall structure of the trial is held constant during its execution, an adaptive trial is designed to take advantage of the stream of information acquired during the study period to trigger specific changes or adaptations in the trial structure according to prespecified data-driven decision rules.[9] Changes that may be triggered include altering the number of treatment arms, the dosage of pharmaceutical agents, or the randomization proportions; the early termination of an arm or subpopulation for a demonstration of efficacy, futility, or harm; or the restriction of the overall study population to focus on subjects who appear to be benefiting most from the experimental therapies (termed "enrichment"). Response-adaptive randomization, in which future subjects are preferentially randomized to the arm(s) that appear most promising based on current data, can improve both the statistical performance and the ethical balance of the trial.[18–21] Trauma is an ideal setting in which to apply adaptive approaches as patient-centered outcomes are often measured in hours to days, leading to a more rapid accrual of information. Advances in Bayesian statistical methodology, including computationally intensive approaches, have facilitated adaptive trial design because the Bayesian inferential model is well suited to analyzing results when changes in the structure of the trial have occurred.

A platform trial is an extension of an adaptive clinical trial design to evaluate multiple treatments simultaneously. Interventions are often administered in combination with the list of available treatment arms changing over time as some are found to be effective, ineffective, or harmful and new treatments become available.[13–15] Further, an adaptive platform trial is an integrated clinical trial infrastructure, which operates under a single master protocol using a coherent and integrated statistical inferential framework.

The term "master protocol" refers to an ongoing and stable clinical trial infrastructure that is one part of the efficiency of the overall platform strategy. A master protocol allows a number of inferentially separate trials to be conducted in series and does so more practically than if a separate trial network and infrastructure were created for each study. A platform trial, however, with an integrated inferential framework, produces *both* operational and statistical efficiencies.

The design typically considers multiple clinically distinct subgroups of patients and allows for the effectiveness of treatments, or even the identity of the most effective treatment, to vary by subgroup. Platform trials often use response-adaptive randomization to efficiently allocate patients to treatments based on the combinations of therapies that appear the most promising, given the subject's baseline characteristics.[15,17] The ability of the platform trial design to address combination treatment strategies and heterogeneity of treatment benefits across subgroups makes this approach particularly impactful in the evaluation of interventions for severely injured subjects.[16]

The platform trial approach increases the efficiency of learning, with every enrolled subject potentially providing information on the effectiveness of multiple therapies, and avoids the waste associated with the startup and breakdown of individual RCTs before and after addressing each therapeutic question (Table 1).[17] Recently, platform trials have been particularly important in rapidly addressing key questions in the care of patients with COVID-19 infection, demonstrating such trial feasibility and value.[24–30]

In this manuscript, we consider the advantages and a few of the challenges associated with the use of an adaptive platform trial to evaluate treatments in the care of both pediatric and adult patients suffering from potentially life-threatening post-traumatic hemorrhage. To consider the value proposition of an adaptive platform trial, we will outline an overall structure for such a platform trial, suggest potential domains of therapies that are of high priority for investigation, and discuss the choice of the primary outcome. Table 2 summarizes how the features of the proposed adaptive platform design address the previously identified challenges associated with conducting an RCT in post-traumatic hemorrhage. An accompanying manuscript will delve into the operational details of an adaptive platform trial for post-traumatic

TABLE 1 Sources of platform trial efficiency[17]

Platform trial characteristic	Associated efficiency
Simultaneous evaluation of multiple therapeutic options within each domain	No requirement to duplicate control subjects for the evaluation of each experimental treatment within a domain
Evaluation of multiple therapeutic domains	Simultaneous investigation of multiple domains of care, reducing the average time and number of enrolled subjects required per result generated. This supports the goal of exposing the minimum number of subjects possible to address each clinical question.
Dynamic set of treatment options	The trial utilizes a dynamic set of treatment options so that there is no stopping or pausing of the trial when a result is generated and minimal start up time when a new treatment is added.
Response-adaptive randomization	The randomization proportions for future subjects are adjusted, after a suitable "burn in" period, so that future subjects are preferentially allocated to the treatment regimens that are most likely to be effective. This increases the rate at which data are generated for the most promising therapies, even though the identity of the most promising therapies cannot be known at the beginning of the trial.[18–20]
Statistical modeling (e.g., hierarchical modeling) to yield efficient estimation of treatment effects within prespecified subgroups	Hierarchical modeling reduces the average mean-square error in the estimation of treatment effects across subgroups, while allowing for flexibility in the extent to which data across subgroups are pooled or considered independently.[22,23]
Ability to replace the control treatment strategy	The control treatment or factor within each domain can be replaced when the standard of care changes, eliminating the need to pause or terminate the trial with improvements in the standard of care.

TABLE 2 Challenges in evaluating therapies in subjects with exsanguinating post-traumatic hemorrhage

Clinical research challenge	Pertinent platform trial feature
Variable mechanisms of injury, sources of bleeding, and injury severity	Estimation of treatment effects separately for prespecified clinically distinct patient subgroups or strata; adjustment for baseline characteristics
Multiple phases and sites of care (e.g., prehospital, emergency department, operating room, intensive care unit)	Trial can accommodate multiple time points at which a patient becomes eligible for a treatment, with the allocation to later treatments only revealed when needed
Simultaneous administration of multiple treatments with the possibility of interactions between treatments	Separate randomization in each domain of care allows simultaneous investigation of multiple therapies; evaluation of efficacy at the level of the regimen (the combination of all assigned treatments or factors) allows for the possibility of interactions or synergy among treatments.
Both early and longer-term outcomes of interest	The primary endpoint will be 6-hour all-cause mortality; however, in cases in which informing clinical care requires consideration of longer-term outcomes, the 28-day all-cause mortality will be considered
Difficulty in obtaining consent will require an emergency exception from informed consent (e.g., 21 CFR 50.24)	The trial will be designed to hold "out the prospect of direct benefit to the subjects" as required in 21 CFR 50.24(a) (3) both through the investigation of promising treatments and through the use of response-adaptive randomization to improve outcomes within the trial
Changes in the effectiveness of care over time; secular trends	Explicit adjustment for time-based trends in the primary inferential model rather than only as a secondary or post-hoc sensitivity analysis
Introduction of new standards of care	If a new standard of care is defined for one of the treatment domains, the prior standard of care can be removed from the trial, and the new standard of care used as the control treatment or factor going forward. This can be accommodated without any pause in the trial or change to the underlying trial and statistical methodology

hemorrhage,[31] and another will address key ethical and regulatory challenges of conducting such a trial in resource-limited settings (including military environments) as well as considerations surrounding the inclusion of children and pregnant women.[32]

2 | THE PROPOSED TRIAL DESIGN

2.1 | Overall structure of the adaptive platform trial

The structure of an adaptive platform trial includes the selection of the patient population; the timing of enrollment, randomization, and assignment of treatments; the domains of therapy that are to be investigated and the specific treatment options within each domain; the primary outcome measure; and the decision rules used at interim analyses.[13] Randomized treatment assignments may be revealed immediately and the treatments administered, or they may remain concealed unless and until they are relevant to the patient (e.g., assignment to a particular intraoperative intervention would only be revealed if the patient was taken to the operating room). The decision rules include criteria for drawing a conclusion regarding the efficacy of a particular treatment (e.g., superiority, non-inferiority, futility, or harm) and updating the randomization proportions for future patients.[13,14,17]

2.2 | Study populations and subgroups

Owing to the ubiquity of major traumatic injuries, we propose to enroll a broad population including both pediatric and adult subjects as well as victims of both penetrating and blunt trauma with signs and symptoms suggestive of potentially life-threatening hemorrhage. The inclusion criteria for the trial will be: (1) a major traumatic injury meeting local criteria for preferential transport to a specialized level I or level II trauma center, or secondary transfer to a specialized center if initially transported to a non-trauma center, (2) evidence of life-threatening hemorrhage, defined either by local standards for initiation of a massive transfusion protocol or a standardized clinical score, and (3) an estimated time-since-injury of ≤6 h.

Exclusion criteria include the following: (1) traumatic cardiac arrest at any time after the injury, (2) inability to either obtain written informed consent from the patient, an appropriate surrogate, or utilize an exception from informed consent in compliance with local requirements, (3) known membership in a group likely to object to one or more study treatments (e.g., Jehovah's Witnesses), (4) prior enrollment in the trial, and (5) neurological injury that is judged to be incompatible with survival.

The inclusion and exclusion criteria are intended to select a broad population of patients suffering from severe post-traumatic hemorrhage. However, it is anticipated that some of the treatments being evaluated will be limited to subgroups of the overall study population. Thus, with respect to the evaluation of a particular intervention, additional exclusion criteria may apply.

TABLE 3 Example treatment domains and factors

Treatment domain	Factors of treatment options within the domain
Transfusion strategy	1. Arm A: (Control) with 1:1:1 plasma: Platelets:RBCs 2. Arm B: Low titer liquid cold stored whole blood (LTOWB) 3. Arm C: Fresh whole blood
Management of coagulopathy	1. Arm A: (Control) plasma (FFP, thawed or liquid) 2. Arm B: Thromboelastography (TEG) guided management 3. Arm C: Fibrinogen concentrate first strategy 4. Arm D: (Back up) Lyophilized plasma 5. Arm E: (Back up) Prehospital freeze-dried plasma w TEG-guided ED management
Hemorrhage control	1. Arm A: (Control) Stop the Bleed Interventions 2. Arm B: Prehospital hemorrhage control with wound packing using hemostatic agents 3. Arm C: Prehospital hemorrhage control with injectable sponges
Management of acute respiratory distress syndrome	1. Arm A: (Control) Low tidal volume ventilation 2. Arm B: ECMO to obviate the need for ventilation 3. Arm C: Anti-inflammatory therapies

2.3 | Treatment domains

The medical therapies assigned to study subjects in a platform trial are organized into the categories of domains, factors, and regimens.[13] A domain is a group of mutually exclusive treatment choices being compared in the trial, typically with each of the active treatments

having the same general therapeutic aim. For example, one domain might be transfusion strategy and the treatments randomized within that domain might be different transfusion thresholds or different choices in the ratios of blood components used in initial resuscitation.[33] Within each domain, the individual treatment options are called "factors." Another domain might be the management of coagulopathy with two factors being the use of fresh-frozen plasma or fibrinogen concentrate, or different methods for monitoring coagulation parameters and responding to deficits.[34] Further examples of domains and factors relevant to the treatment of post-traumatic hemorrhage are listed in Table 3. In general, the factors across different domains can be assigned independently, resulting in a factorial structure of the trial. It is also possible to implement restricted randomization, that is designating specific combinations of factors across domains as unallowed. The set of all assigned treatment factors across all randomized domains is called the treatment "regimen" for the patient. Thus, each patient receives a single regimen consisting of a single factor selected from each of the treatment domains.[13]

Some domains may only be relevant to specific subgroups of patients, for example, those with a concomitant blunt head injury, or may only be relevant to patients that reach different treatment milestones, for example, requiring mechanical ventilation or surviving admission to the ICU. In the latter case, characteristics used in stratified randomization[35] within a specific domain may only be apparent later in the patient's course, requiring a second randomization time point and a new "time zero" for the evaluation of those later interventions.

2.4 | Outcome measures

The timing and underlying cause of death for the fatally injured trauma patient are highly variable. In selecting a primary outcome measure with the goal of being sensitive to improvements in the management of exsanguinating hemorrhage, it is important to select an outcome and timing of measurement for that outcome that captures the effects of hemorrhage while, to the extent possible, minimizing the influences of competing risks: other events (e.g., death from neurotrauma) that make it impossible to observe the benefit of treatment for hemorrhage.[36] Based on these considerations and substantial empirical evidence, a consensus conference convened by the National Institutes of Health National Heart Lung and Blood Institute, and the US Department of Defense recommended a relatively short-term primary endpoint in studies of post-traumatic hemorrhagic shock, namely 6-h all-cause mortality.[37,38] This choice emphasizes death from a hemorrhage while avoiding the subjective post hoc classification of deaths as being due to hemorrhage versus other mechanisms while reducing contamination from death due to neurotrauma which tends to occur later. Thus, all-cause mortality at 6 h from initial enrollment is the primary endpoint for the proposed trial.

The choice of a proximate endpoint—6-h all-cause mortality—may raise concerns about the possibility that a treatment may paradoxically improve short-term outcomes but worsen longer term, more patient-centered, outcomes. Further, the impact of a positive trial result on clinical care may be limited without information on longer-term outcomes. To address these issues the key secondary outcome of the trial will be 28-day, all-cause mortality.[38] Additional secondary outcomes, for example, survival time, may be considered as well.

It may be desirable to investigate therapies that address complications that only occur after a 6-h time frame (e.g., respiratory or infectious complications). It would be necessary to identify suitable longer-term outcomes for such treatment domains.

2.5 | Randomization

Patients who meet enrollment criteria will be randomized to treatment options within each of the domains for which the patient is eligible based on their baseline characteristics. Patients may also be assigned treatments in domains (e.g., operating room interventions) for which they are not yet eligible, with the assignments concealed until the patient meets the eligibility criteria for the domain. Although a patient who is not yet eligible for a domain may be assigned a treatment, they would not be included in an analysis of that domain unless they become eligible, and the treatment assignment is revealed.

Response-adaptive randomization will be utilized to increase the statistical efficiency of the trial by increasing the fraction of enrolled patients who receive the treatments that are of most interest because they appear to be performing better and to improve the outcomes of patients enrolled in the trial.[18–20] After a period of fixed randomization (termed the "burn in" period) across factors within each domain,[18] response-adaptive randomization will be applied at the level of the regimen, with the probability of assignment based on the Bayesian probability that the regimen is the optimal choice for a patient with the particular set of baseline characteristics. The randomization probabilities will be updated during interim analyses as the trial progresses. Even after

response-adaptive randomization is initiated, however, a constant fraction of patients will be allocated to the current standard of care in each treatment domain to ensure the inferential statistical model can effectively detect and adjust for secular trends, for example, changes over time in the characteristics of the subject population or in the effectiveness of the standard of care.[19]

2.6 | Inferential model

The inferential statistical model for the trial will be based on a Bayesian regression model of subject outcomes after adjustment for baseline characteristics. The inferential model will also account for the other assigned treatments the subject received either simultaneously or previously. While one feature of a Bayesian approach would be the ability to incorporate prior information in estimating treatment effects,[10] non-informative or diffuse priors will be used so that estimates are determined overwhelmingly by the randomized experimental data.[22] In essence, the Bayesian "machinery" is being used only to provide a rigorous quantitative method for the frequent updating of information as new data become available. The statistical model will yield both posterior probability density functions summarizing the effect of each treatment or factor within a domain on subject outcomes, as well as estimates of the probability that each treatment regimen—the collection of all individual treatment options across domains—is the optimal regimen for patients within each of the primary strata. From this model, the probability that each factor is optimal within its respective domain for a defined subgroup of patients will be obtained by summing the Bayesian posterior probabilities that each of the regimens is optimal across all the regimens that include that factor. By summing up the probabilities that each combination of treatments that includes the factor is optimal, we obtain the total probability that the factor is optimal, essentially averaging across all other treatment domains. The posterior probability associated with each factor will then be used to implement the interim decision rules that define the adaptive trial design. The decision rules are designed to efficiently select the most effective treatments. The inferential model will also yield the probability that each experimental factor in a domain is superior to the control and the probability that each factor is superior to the control by a given amount (e.g., a threshold effect size expressed as an odds ratio).

To address the challenges of efficient estimation of treatment effects across multiple patient subgroups, hierarchical modeling will be used.[23] When a treatment effect is consistent across subgroups, this approach results in the borrowing of information across subgroups, resulting in more precise estimates of treatment effects. In contrast, when the treatment effect appears more heterogeneous across subgroups, the estimate of treatment effect in each subgroup is based primarily on the data from that subgroup. Thus, estimates of the treatment effects in a subgroup will be based on the outcomes in that subgroup, as well as the consistency of the apparent treatment effects across subgroups.[23,39]

Because the platform trial is intended to continue over an extended period, with likely improvements in the effectiveness of the existing standard of trauma care, the inferential model will include a statistical adjustment for time to allow for secular trends.[40] This adjustment, along with randomization ratios designed to maintain a sufficient and stable allocation to the standard of care arm within each domain,[19] helps to ensure valid estimation of treatment effects despite variations in the patient populations and concomitant therapies over time. This modeling strategy has been used successfully in recent COVID-19 platform trials.[24–30]

A related issue is the choice of control patients to be included in comparisons when estimating the effects of treatments. For experimental treatments that enter the platform trial sometime after the start of the trial, the concurrent controls are patients that, at the time of their randomization, could have been assigned to that treatment. Control patients randomized before a treatment enters the trial, or at study sites that do not offer the treatment, are considered to be non-concurrent controls. Using only concurrent control patients for estimates of the treatment effects of newly added treatments minimizes the effect of a time trend caused by changes in practice, patient population, or seasonal trends.[41] However, the use of non-concurrent control patient data along with model-based approaches to adjust for time trends can lead to more precise estimates of treatment effects.[17,42–44] This approach would be particularly helpful in comparisons and evaluating treatments for which the eligible patient population is small.

Use of non-concurrent control patient data may be less controversial in deriving estimates of risk to be used in risk adjustment analyses of the trial treatments. Such risk adjustment is useful for trials involving heterogeneous populations, such as trauma, in which chance imbalance in treatment groups can happen even without changes in the patient population. In such settings, adjusting for baseline risk is desirable to reduce bias in estimates of treatment effects. In a platform trial, a risk model could first be derived which could include data from non-concurrent controls and other treatment arms. The resulting model could then be used to calculate risk estimates for patients randomized to treatments to be

analyzed and concurrent controls to derive risk-adjusted estimates of treatment effects.

2.7 | Interim analyses and decision rules

At each interim analysis of the trial, a snapshot of the clinical database will be taken, and the data analyzed using the Bayesian inferential model. A minimum clinically important difference (MCID)[45] for an improvement in survival will be defined, however, in this setting the magnitude of the treatment effect sought by the trial will be influenced by limitations in the expected rates of trial enrollment and outcomes. The results of the inferential model will be a probability that each factor is superior to control, is superior to control by at least the MCID, or is the optimal treatment choice within each domain. These probabilities will be determined for each patient subgroup or stratum using the hierarchical approach and the interim decision rules will be based on these probabilities. The precise decision rules and the associated probability thresholds for each treatment domain will be determined by the trial steering committee prior to the initiation of the trial. They will be informed by computer simulation[13] of the trial design while considering the specific treatment options and current standard of care within each domain. The general structure of the domain-specific decision rules is expected to be as follows, with typical probability thresholds included as examples, and with each rule applying within a patient subgroup or stratum:

1. *Stopping for futility*. Randomization to a particular factor within a domain will be irreversibly terminated if the Bayesian posterior probability that the factor is superior to the control factor by at least the MCID is less than .01. Alternatively, if there is not a clearly identified standard of care/control treatment in the domain, a factor may be terminated if the probability that it is the optimal factor is less than .01.
2. *Stopping for demonstration of efficacy*. Randomization to a particular factor within a domain will be terminated and efficacy considered demonstrated if the Bayesian posterior probability that the factor is superior to the control factor is greater than .99. Otherwise, if there is not a clearly identified control treatment in the domain, a factor may be terminated, and efficacy considered demonstrated if the probability that it is the optimal factor among all choices is greater than .99. If a factor is demonstrated to be superior to the control, the existing control will be dropped from the trial and the superior treatment will become the new control therapy.
3. *Stopping due to the maximum sample size being reached*. Randomization to a particular factor within a domain will be terminated if the maximum allowed sample size for that factor (if specified) has been reached. A limit on the sample size may be implemented for logistical reasons, for example, a limitation in the availability of the agent, or if it is deemed futile or poor use of resources to continue allocation to the factor if efficacy has not already been demonstrated once the maximum sample size is reached. This latter criterion for the maximum sample size can be determined in a manner analogous to a traditional sample size calculation.
4. *Closing of a domain*. If, based on the above decision rules, fewer than two available factors remain in the domain, then the domain will be closed. However, if it is expected that a new factor in the domain will become available in the near term, the domain may be suspended while awaiting the introduction of the new factor and a resumption of randomization.
5. *Continue with revision to randomization proportions*. If the domain remains open, meaning there are at least two remaining factors in the domain available for randomization, then the randomization proportions within the domain will be revised according to the probability that each factor is an optimal choice. If the probability that a factor is the optimal choice falls below .05, then no patients will be allocated to that factor to avoid randomizing patients to treatment strategies that do not appear favorable based on the current data. However, the factor may be reintroduced in later randomizations if accumulating experience with the other factors results in a probability of being optimal rising above .05 at a future interim analysis.

If any of the statistical triggers 1 through 4 above are met, then the results of the interim analysis and the application of the decision rules will be reviewed by an independent data and safety monitoring board (DSMB) before any action is taken. The DSMB will make a recommendation regarding the implementation of the decision rule to the trial's steering committee. If none of the statistical triggers are met, then the randomization probabilities will be updated and the DSMB informed regarding the updated randomization probabilities.

2.8 | Simulation-based trial design

Figure 1 visualizes the overall framework of the proposed adaptive platform trial, defined by the features outlined above. The detailed statistical design of this trial framework, including the details of the Bayesian hierarchical

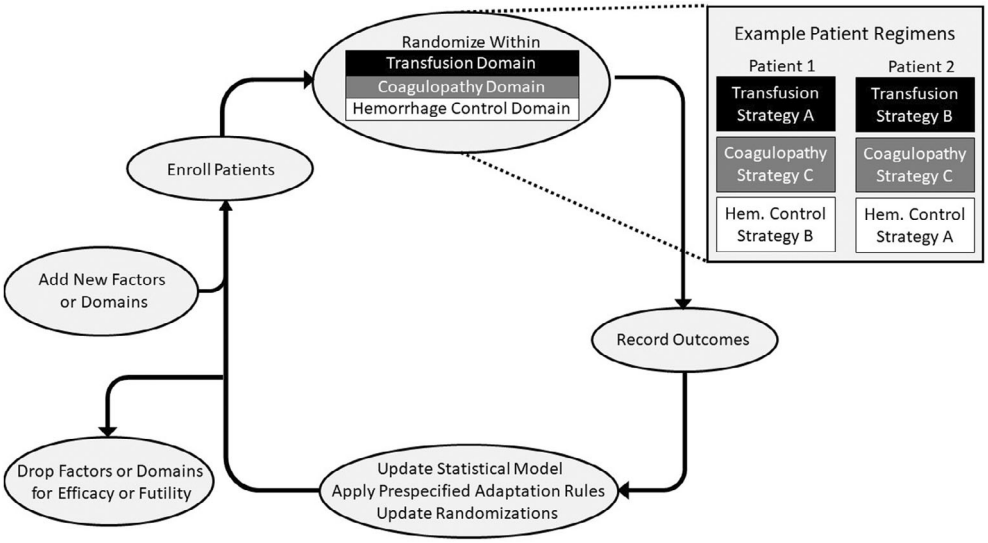

FIGURE 1 This figure illustrates the overall structure for the proposed platform trial, with example domains for illustration. The process of enrolling patients, randomization, treatment, outcome assessment, updating of the statistical model, and application of adaptive decision rules and response-adaptive randomization is intended to be a continual, seamless process. Each of the domains of care, i.e., transfusion strategy, management of coagulopathy, and management of hemorrhage would have several treatment options or factors to which patients are randomized. The factors or treatment options within each domain are denoted A, B, or C in this schematic.

model and the structure and thresholds of the decision rules, will be determined by Monte Carlo computer simulation of the trial design across a wide range of possible scenarios.[31] The scenarios to be considered, and for which the trial performance will be evaluated, will vary in the assumed efficacy of the interventions and the heterogeneity of the treatment effects across subgroups, outcomes rates, enrollment rates, and other parameters. For example, type I error control will be demonstrated under a variety of null scenarios with the assumption that at least one of the experimental treatments is no better than the control/standard of care. This will allow us to choose a trial design that appropriately balances the required sample size against the desire to generate estimates of treatment effects that are sufficiently precise and specific to clinically important subgroups of patients to support both clinical and regulatory decision-making. In general, the type I error rate for each therapeutic question will be matched to what would be required for a single trial addressing the same therapeutic question. While Monte Carlo computer simulation will be used to evaluate the type I (false positive) error risk associated with the proposed decision rules, with the possibility of adjusting the thresholds (e.g., .01 and .99) accordingly, we note that these proposed thresholds are similar to those used in the REMAP-CAP platform trial in COVID.[24–30]

The simulation also has the potential to address concerns that have been raised regarding sub-optimal statistical characteristics associated with poorly designed adaptive trials (e.g., inflation of type I error risk, excessive bias in the estimation of treatment effects, vulnerability to effects of secular changes in the patient population or outcomes). Simulation of adaptive designs prior to trial implementation can quantify these threats and facilitate design optimization (e.g., adequate minimum sample size, avoiding overly aggressive response adaptive randomization, use of concurrent control subjects in the primary estimation of treatment effects) to ensure the desired statistical performance is achieved.

3 | DISCUSSION

While an adaptive platform trial has not, to our knowledge, been performed in a critically injured patient population, recent experience during the COVID-19 pandemic has demonstrated both the feasibility and immediate scientific value of this approach. Further, conducting such a trial is an opportunity to generate data on the treatment of populations who are typically excluded from such trials, for example, pediatric patients and pregnant women.[32]

Determining the scale of the trial (e.g., the number of participating sites, number of domains to be considered, and the number of factors in each domain) involves practical and statistical considerations. Not all trial sites may participate in all domains, depending on local site capability to offer specific treatments. While increasing the number of domains and factors will generally result in a long time to answer the first therapeutic question, there is an increase in overall efficiency with the addition of

domains and factors, especially compared to an equivalent series of standalone trials each evaluating a single factor (or even each evaluating all factors within single domains). Many platform trials grow in scale over time, allowing a greater number of therapeutic questions to be posed and answered quickly. The larger the number of centers and the faster the pace of enrollment, the shorter the time required to answer each therapeutic question.

The successful implementation of the proposed platform trial, including providing the necessary oversight and governance, will require a vibrant collaboration across multiple investigators, institutions, and settings. Multiple potential hurdles exist, however, including overcoming challenges related to securing perpetual funding, identifying eligible patients in often chaotic prehospital and emergency department settings, ensuring effective and ethical consent processes, implementing real-time randomization and initiation of assigned therapies, and achieving complete and accurate capture of outcomes. Independent oversight from a multidisciplinary data and safety monitoring board with a thorough understanding of the trial design will also be required. A number of these complex issues are addressed in companion manuscripts.[31,32]

We acknowledge that investigating the effectiveness of therapies—both current and novel—for the treatment of patients with life-threatening hemorrhagic shock is a daunting task. Variability in patient injury, hemodynamic status, location of care and available resources, and the complexity of administering multifaceted and multidisciplinary care in a time-sensitive setting all create additional challenges and barriers. However, failing to compare treatments using a rigorous and prospective clinical trial strategy would subject our future patients to the same unproven therapies and unwarranted practice variation that we continue to struggle with today.

In completing the statistical design of the clinical trial and the detailed planning of clinical care and associated data collection, collaborative discussions with regulatory personnel will be critical. The intent to utilize the emergency exception from informed consent for enrollment will require the filing of an Investigational New Drug Application (IND) for products regulated either by the FDA Center for Drug Evaluation and Research or by the Center for Biologics Evaluation and Research or an Investigational Device Exemption (IDE) for devices regulated by the Center for Devices and Radiological Health.[46] A key goal of the regulatory interactions will be to ensure that the specified trial design, if it generates definitive results, will be deemed of sufficient methodological rigor to inform regulatory decision-making. In many cases, this will likely be the most efficient way, both in terms of time and cost, to evaluate promising new treatments for patients with life-threatening post-traumatic hemorrhagic shock.

4 | CONCLUSION

An adaptive platform trial evaluating treatments for patients with life-threatening post-traumatic hemorrhage has the potential to accelerate the discovery of more effective treatments for this common and devastating disease. While the challenges of launching such a trial are substantial, they can be successfully addressed if the trauma research community coalesces around our common goal of finding the best ways to take care of these patients.

CONFLICT OF INTEREST

JT is a Medical and Statistical Scientist at Berry Consultants, LLC, a statistical consulting firm that specializes in the design, implementation, oversight, and interpretation of Bayesian adaptive trials, including platform trials. MAS was previously a member of the Patient Blood Management Committee of AABB. FXG has received DoD contract to fund the LITES clinical trial network. HW is the Editor in Chief of the Journal of the American College of Emergency Physicians and has received grant support from NIH and DoD. JOJ has received grant support from NIH, DoD, and NIHR; is a consultant for CSL Behring and Cellphire; and has received study support from CSL Behring, RevMedX, Infrascan, and Prytime Medical. WJM is a Medical and Statistical Scientist at Berry Consultants, LLC. RJL is the Senior Medical Scientist at Berry Consultants, LLC.

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REFERENCES

1. National Center for Health Statistics, Centers for Disease Control and Prevention. Leading Causes of Death and Numbers of Deaths, by Age: United States, 1980 and 2018. Available at http://www.cdc.gov/nchs/hus/contents2019.htm#Table-007 accessed December 1, 2021.
2. Tisherman SA, Stein DM. ICU Management of Trauma Patients. Crit Care Med. 2018;46(12):1991–7. https://doi.org/10.1097/CCM.0000000000003407
3. Jones CM, Cushman JT, Lerner EB, Fisher SG, Seplaki CL, Veazie PJ, et al. Prehospital trauma triage decision-making: a model of what happens between the 9-1-1 call and the hospital. Prehosp Emerg Care. 2016;20(1):6–14. https://doi.org/10.3109/10903127.2015.1025157
4. Schafer N, Driessen A, Frohlich M, Sturmer EK, Maegele M, TACTIC partners. Diversity in clinical management and

protocols for the treatment of major bleeding trauma patients across European level I trauma Centres. Scand J Trauma Resusc Emerg Med. 2015;23:74. https://doi.org/10.1186/s13049-015-0147-6
5. Spinella PC. Zero preventable deaths after traumatic injury: an achievable goal. J Trauma Acute Care Surg. 2017;82(6S Suppl 1):S2–8. https://doi.org/10.1097/TA.0000000000001425
6. Carroll SL, Dye DW, Smedley WA, Stephens SW, Reiff DA, Kerby JD, et al. Early and prehospital trauma deaths: who might benefit from advanced resuscitative care? J Trauma Acute Care Surg. 2020;88(6):776–82. https://doi.org/10.1097/TA.0000000000002657
7. Angus DC, Chang CH. Heterogeneity of treatment effect: estimating how the effects of interventions vary across individuals. JAMA. 2021;326(22):2312–3. https://doi.org/10.1001/jama.2021.20552
8. Champion HR, Fingerhut A, Escobar MA, Weiskopf RB. The role of data and safety monitoring in acute trauma resuscitation research. J Am Coll Surg. 2007;204(1):73–83. https://doi.org/10.1016/j.jamcollsurg.2006.10.024
9. US Food and Drug Administration. Adaptive Designs for Clinical Trials of Drugs and Biologics Guidance for Industry. Available at https://www.fda.gov/media/78495/download. Accessed November 19, 2021.
10. Berry S, Carlin BP, Lee JJ, Muller P. Bayesian adaptive methods for clinical trials, Chapman & Hall/CRC biostatistics series. 2010.
11. Meurer WJ, Lewis RJ, Tagle D, Fetters MD, Legocki L, Berry S, et al. An overview of the adaptive designs accelerating promising trials into treatments (ADAPT-IT) project. Ann Emerg Med. 2012;60(4):451–7. https://doi.org/10.1016/j.annemergmed.2012.01.020
12. Bhatt DL, Mehta C. Adaptive designs for clinical trials. N Engl J Med. 2016;375(1):65–74. https://doi.org/10.1056/NEJMra1510061 PMID: 27406349.
13. Adaptive Platform Trials Coalition. Adaptive platform trials: definition, design, conduct and reporting considerations. Nat Rev Drug Discov. 2019;18(10):797–807. https://doi.org/10.1038/s41573-019-0034-3 Epub 2019 Aug 28. Erratum in: Nat Rev Drug Discov. 2019 Sep 10;: PMID: 31462747.
14. Woodcock J, LaVange LM. Master protocols to study multiple therapies, multiple diseases, or both. N Engl J Med. 2017;377(1):62–70. https://doi.org/10.1056/NEJMra1510062 PMID: 28679092.
15. Berry SM, Connor JT, Lewis RJ. The platform trial: an efficient strategy for evaluating multiple treatments. JAMA. 2015;313(16):1619–20. https://doi.org/10.1001/jama.2015.2316 PMID: 25799162.
16. Tolles J, Lewis RJ (2018). Adaptive and platform trials in remote damage control resuscitation. J Trauma Acute Care Surg, Jun;84(6S Suppl 1):S28-S34. doi: https://doi.org/10.1097/TA.0000000000001904. PMID: 29554037
17. Saville BR, Berry SM. Efficiencies of platform clinical trials: a vision of the future. Clin Trials. 2016;13(3):358–66. https://doi.org/10.1177/1740774515626362 Epub 2016 Feb 17. PMID: 26908536.
18. Viele K, Saville BR, McGlothlin A, Broglio K. Comparison of response adaptive randomization features in multiarm clinical trials with control. Pharm Stat. 2020;19(5):602–12. https://doi.org/10.1002/pst.2015 Epub 2020 Mar 21. PMID: 32198968.
19. Viele K, Broglio K, McGlothlin A, Saville BR. Comparison of methods for control allocation in multiple arm studies using response adaptive randomization. Clin Trials. 2020;17(1):52–60. https://doi.org/10.1177/1740774519877836 Epub 2019 Oct 19. PMID: 31630567.
20. Meurer WJ, Lewis RJ, Berry DA. Adaptive clinical trials: a partial remedy for the therapeutic misconception? JAMA. 2012;307(22):2377–8. https://doi.org/10.1001/jama.2012.4174
21. London AJ. Learning health systems, clinical equipoise and the ethics of response adaptive randomization. J Med Ethics. 2018;44:409–15.
22. US Food and Drug Administration Guidance for the Use of Bayesian Statistics in Medical Device Clinical Trials. Available at https://www.fda.gov/regulatory-information/search-fda-guidance-documents/guidance-use-bayesian-statistics-medical-device-clinical-trials. Accessed April 29, 2022.
23. Gelman A, Carlin JB, Stern HS, Rubin DB. Bayesian Data Analysis. 2nd ed. Boca Raton: Texts in Statistical Science. Chapman & Hall/CRC; 2003.
24. UPMC REMAP-COVID Group, on behalf of the REMAP-CAP Investigators. Implementation of the randomized embedded multifactorial adaptive platform for COVID-19 (REMAP-COVID) trial in a US health system-lessons learned and recommendations. Trials. 2021;22(1):100. https://doi.org/10.1186/s13063-020-04997-6 Erratum in: Trials. 2021 Feb 16;22(1):145. PMID: 33509275; PMCID: PMC7841377.
25. Angus DC, Berry S, Lewis RJ, Al-Beidh F, Arabi Y, van Bentum-Puijk W, et al. The REMAP-CAP (randomized embedded multifactorial adaptive platform for community-acquired pneumonia) study. Rationale and design. Ann Am Thorac Soc. 2020;17(7):879–91. https://doi.org/10.1513/AnnalsATS.202003-192SD PMID: 32267771; PMCID: PMC7328186.
26. ATTACC Investigators; ACTIV-4a Investigators; REMAP-CAP Investigators, Lawler PR, Goligher EC, Berger JS, Neal MD, BJ MV, et al. Therapeutic anticoagulation with heparin in non-critically ill patients with Covid-19. N Engl J Med. 2021;385(9):790–802. https://doi.org/10.1056/NEJMoa2105911 Epub 2021 Aug 4. PMID: 34351721; PMCID: PMC8362594.
27. REMAP-CAP Investigators; ACTIV-4a Investigators; ATTACC Investigators, Goligher EC, Bradbury CA, McVerry BJ, Lawler PR, Berger JS, et al. Therapeutic anticoagulation with heparin in critically ill patients with Covid-19. N Engl J Med. 2021;385(9):777–89. https://doi.org/10.1056/NEJMoa2103417 Epub 2021 Aug 4. PMID: 34351722; PMCID: PMC8362592.
28. Writing Committee for the REMAP-CAP Investigators, Estcourt LJ, Turgeon AF, ZK MQ, McVerry BJ, Al-Beidh F, et al. Effect of convalescent plasma on organ support-free days in critically ill patients with COVID-19: a randomized clinical trial. JAMA. 2021;326(17):1690–702. https://doi.org/10.1001/jama.2021.18178 PMID: 34606578; PMCID: PMC8491132.
29. Arabi YM, Gordon AC, Derde LPG, Nichol AD, Murthy S, Beidh FA, et al. Lopinavir-ritonavir and hydroxychloroquine for critically ill patients with COVID-19: REMAP-CAP randomized controlled trial. Intensive Care Med. 2021;47(8):867–86. https://doi.org/10.1007/s00134-021-06448-5 Epub 2021 Jul 12. PMID: 34251506; PMCID: PMC8274471.
30. Angus DC, Derde L, Al-Beidh F, Annane D, Arabi Y, Beane A, et al. Effect of hydrocortisone on mortality and organ support in patients with severe COVID-19: the REMAP-CAP COVID-

19 corticosteroid domain randomized clinical trial. JAMA. 2020;324(13):1317–29. https://doi.org/10.1001/jama.2020.17022 PMID: 32876697; PMCID: PMC7489418.
31. del Junco DJ, Neal MD, Shackelford SA, Spinella PC, Guyette FX, Sperry JL, et al. An adaptive platform trial for evaluating treatments in patients with life-threatening hemorrhage from traumatic injuries: planning and execution. Transfusion. 2022.
32. Goldkind SF, Brosch LR, Lewis RJ, Pedroza C, Spinella PC, Shackelford SA, et al. An adaptive platform trial for evaluating treatments in patients with life-threatening hemorrhage from traumatic injuries: ethical and US regulatory considerations. Transfusion. 2022.
33. Holcomb JB, Tilley BC, Baraniuk S, Fox EE, Wade CE, Podbielski JM, et al. Transfusion of plasma, platelets, and red blood cells in a 1:1:1 vs a 1:1:2 ratio and mortality in patients with severe trauma: the PROPPR randomized clinical trial. JAMA. 2015;313(5):471–82. https://doi.org/10.1001/jama.2015.12
34. Callum J, Farkouh ME, Scales DC, Heddle NM, Crowther M, Rao V, et al. Effect of fibrinogen concentrate vs cryoprecipitate on blood component transfusion after cardiac surgery: the FIBRES randomized clinical trial. JAMA. 2019;322(20):1966–76. https://doi.org/10.1001/jama.2019.17312
35. Broglio K. Randomization in clinical trials: permuted blocks and stratification. JAMA. 2018;319(21):2223–4. https://doi.org/10.1001/jama.2018.6360
36. Austin PC, Lee DS, Fine JP. Introduction to the analysis of survival data in the presence of competing risks. Circulation. 2016;133(6):601–9. https://doi.org/10.1161/CIRCULATIONAHA.115.017719 PMID: 26858290; PMCID: PMC4741409.
37. Spinella PC, El Kassar N, Cap AP, Kindzelski AL, Almond CS, Barkun A, et al. Hemostasis trials outcomes working group. Recommended primary outcomes for clinical trials evaluating hemostatic blood products and agents in patients with bleeding: proceedings of a National Heart Lung and blood institute and US Department of defense consensus conference. J Trauma Acute Care Surg. 2021;91(2S Suppl 2):S19–25. https://doi.org/10.1097/TA.0000000000003300 PMID: 34039915.
38. Holcomb JB, Moore EE, Sperry JL, Jansen JO, Schreiber MA, Del Junco DJ, et al. Evidence-based and clinically relevant outcomes for hemorrhage control trauma trials. Ann Surg. 2021;273(3):395–401. https://doi.org/10.1097/SLA.0000000000004563 PMID: 33065652.
39. Kwok H, Lewis RJ. Bayesian hierarchical modeling and the integration of heterogeneous information on the effectiveness of cardiovascular therapies. Circ Cardiovasc Qual Outcomes. 2011;4(6):657–66. https://doi.org/10.1161/CIRCOUTCOMES.111.960724 PMID: 22085987.
40. Berry SM, Reese CS, Larkey PD. Bridging different eras in sports. J Am Stat Assoc. 1999;94(447):661–76. https://doi.org/10.1080/01621459.1999.10474163
41. Park JJH, Detry MA, Murthy S, Guyatt G, Mills EJ. How to use and interpret the results of a platform trial: Users' guide to the medical literature. JAMA. 2022;327(1):67–74. https://doi.org/10.1001/jama.2021.22507
42. Elm JJ, Palesch YY, Koch GG, Hinson V, Ravina B, Zhao W. Flexible analytical methods for adding a treatment arm mid-study to an ongoing clinical trial. J Biopharm Stat. 2012;22(4):758–72. https://doi.org/10.1080/10543406.2010.528103
43. Villar SS, Bowden J, Wason J. Response-adaptive designs for binary responses: how to offer patient benefit while being robust to time trends? Pharm Stat. 2018;17(2):182–97. https://doi.org/10.1002/pst.1845
44. Lee KM, Wason J. Including non-concurrent control patients in the analysis of platform trials: is it worth it? BMC Med Res Methodol. 2020;20:165. https://doi.org/10.1186/s12874-020-01043-6
45. McGlothlin AE, Lewis RJ. Minimal clinically important difference: defining what really matters to patients. JAMA. 2014;312(13):1342–3. https://doi.org/10.1001/jama.2014.13128
46. Code of Federal Regulations Title 21 50.24(d). Available at: https://www.accessdata.fda.gov/scripts/cdrh/cfdocs/cfcfr/cfrsearch.cfm?fr=50.24. Accessed November 28, 2021.

How to cite this article: Tolles J, Beiling M, Schreiber MA, Del Junco DJ, McMullan JT, Guyette FX, et al. An adaptive platform trial for evaluating treatments in patients with life-threatening hemorrhage from traumatic injuries: Rationale and proposal. Transfusion. 2022;62(S1):S231–S241. https://doi.org/10.1111/trf.16957