Adaptive and platform trials in remote damage control resuscitation

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ABSTRACT: The traditional approach to clinical trial design requires assuming precise values for multiple unknown parameters, resulting in a trial design that is unlikely to perform well if one or more of those assumptions turn out to be incorrect. During conduct of the trial, trial characteristics are often held fixed, even if incoming data suggest that one or more design assumptions were incorrect. This leads to an increased risk of a failed trial. In contrast, an adaptive clinical trial is designed to take advantage of partial, incoming data during the conduct of the trial, modifying key clinical trial characteristics according to prespecified rules, in order to avoid a failed or inconclusive trial, improve statistical efficacy, better treat patients within the trial, or achieve other scientific or ethical goals. The concept of an adaptive trial can be expanded to a platform trial, a clinical trial that is intended to evaluate multiple treatments or combinations of treatments, often for patients with any of a group of related diseases, and to continue beyond the evaluation of any particular treatment. Platform trial design strategies can be applied to the problem of finding the best treatment strategy for patients suffering from posttraumatic hemorrhagic shock. We present the rationale and considerations surrounding adaptive and platform trial design and apply these concepts to the problem of investigating strategies for remote damage control resuscitation. (J Trauma Acute Care Surg. 2018;84: S28–S34. Copyright © 2018 Wolters Kluwer Health, Inc. All rights reserved.)

KEY WORDS: Adaptive trials; clinical trial design; hemorrhagic shock; platform trials; remote damage control resuscitation.

Traditionally, the design of a prospective randomized clinical trial is based on key assumptions regarding the hoped-for treatment effect, expected event rates, the effective dose of an experimental medication, and the most responsive target patient population. These assumptions are almost universally founded on sparse preliminary data or expert opinion and are therefore prone to both random error and overly optimistic predictions. When using a traditional “fixed” approach to clinical trial design, the design decisions driven by these assumptions cannot be changed after the start of patient enrollment without compromising the statistical validity of the trial. Thus, trials may be too small and underpowered if the treatment effect is overestimated or a truly beneficial treatment may not be identified if the most responsive patient population was not selected by the inclusion and exclusion criteria. Approximately 40% of all Phase III trials fail to demonstrate a treatment effect; this is likely due, in part, to basing clinical trial designs on assumptions that, ultimately, turn out not to be true. The large number of inconclusive or failed trials—trials that fail to give a clear answer to their primary questions—incurs an enormous cost, both in monetary and human terms. We need to design clinical trials that are more efficient and flexible in order to increase the chance of success, to ensure fewer resources are expended when promising treatments turn out to be ineffective, and to ensure trials provide clear answers to the most important clinical questions.

After a clinical trial is launched and patient outcomes begin to accrue, these data decrease the uncertainty in the assumed parameters that drove the initial clinical trial design. Adaptive clinical trials take advantage of this accumulating information to compensate for uncertainty in the initial design assumptions by allowing trial parameters to be adjusted, according to prespecified rules and accumulating outcome data, during the conduct of the trial. This can improve the statistical efficiency or ethical balance of the trial. The general framework for an adaptive trial, shown in Figure 1, begins with the assignment of initial parameters. This is followed by analysis of data at predetermined interim points and subsequent adjustment of trial parameters according to predefined rules. Examples of specific types of adaptations that can be applied within this general trial structure are listed in Table 1. A group sequential trial design, such as an O'Brien-Fleming design, is a simple type of adaptive trial where the only adaptation used is early stopping for an observed positive treatment effect. More broadly, the “art” of adaptive trial design lies in selecting a relatively small number of adaptations that are as effective as possible in mitigating the risks that arise from the uncertainty that exists at the time of trial design. Many adaptive trials are designed using Bayesian statistical methods. Although a full discussion of Bayesian statistical theory is beyond the scope of this article, Bayesian logic is familiar to most clinicians. The phrases “pretest probability” and “posttest probability,” often used with respect to the interpretation of clinical test results, are examples of the application of Bayes theory. The “posttest probability” in the clinical setting represents the clinician’s estimate of the probability that a disease is present based on the history of present illness, physical examination, and so on. The laboratory test or imaging study...
provides data, which, together with study’s test characteristics expressed as a likelihood ratio, can be used to calculate a posterior or “posttest” probability of the disease’s presence. In essence, Bayes theory provides a coherent way to update prior information with new data to yield an updated description of the state of knowledge.

Adaptive clinical trials rely on our ability to update frequently quantitative representations of evidence, including the uncertainty in that evidence, and Bayesian methods are ideal for this process. Bayesian methods are also ideal for addressing questions regarding the probabilities of future events, for example, what is the probability the trial will be positive if it is continued to the planned maximum sample size? Such predictive probabilities can be highly useful in defining decision rules for early stopping for both success and for futility. Trials that use Bayesian statistics can be designed to conform to traditional frequentist Type I error rate and power (i.e., frequentist operating characteristics) requirements (see “Adaptive Trials: Disadvantages and Misconceptions”).

Response Adaptive Randomization
Response-adaptive randomization (RAR) refers to a type of adaptation in which the randomization proportions applied to future patients enrolled in the clinical trial depend on the outcomes of the patients who have already been enrolled. Often, but not always, RAR is used to preferentially randomize subjects to the better-performing arm of a clinical trial. With this approach, the trial begins with equal allocation between all arms because, at the beginning, there are no data from which to learn. At each interim analysis thereafter, the enrollment allocation is adjusted; a simple example of such an adjustment would be to make randomization directly proportional to the Bayesian posterior probability that each arm is the best of the experimental treatment arms. On average, when the experimental treatment arms have different efficacies, this approach can increase the number of subjects who achieve good outcomes while participating in the trial because it will preferentially allocate patients to better-performing arms. Some have suggested that this means adaptive trials with RAR treat subjects more ethically than nonadaptive trials because they offer a greater chance of participant benefit and a partial remedy for the therapeutic misconception. This strategy has several statistical advantages as well, including a more precise estimate of treatment effect in the arms of interest and faster regression to the mean in arms whose initial good performance is due to random fluctuation. The control proportion of patients should generally remain constant, as decreasing the size of the control arm can adversely affect statistical efficiency. This greatly reduces the advantages of RAR in two-arm trials; its usefulness is much greater in trials with three or more arms (see “Adaptive Trials: Disadvantages and Misconceptions”).

The logical extension of response-adaptive adjustment of subject allocation is that some arms may stop enrolling altogether because of either a very low or very high probability of success. This is referred to as “arm dropping” or “early stopping” (either for futility or success). An example of early stopping rules can be found in the I-SPY 2 Phase II trial of...
neoadjuvant therapy for breast cancer, which contains a provision for early stopping for both futility and success. The trial uses complete pathologic response of tumor as a surrogate endpoint for patient survival. Drugs with a low predictive probability of success based on observed rates of pathologic response are dropped from the trial. Because most drugs that enter Phase II trials will not ultimately be effective, early stopping for futility prevents resources from being wasted on unpromising treatments. If an investigational drug in I-SPY 2 is found to have greater than an 85% predicted probability of success in a subsequent Phase III trial, it is "graduated" for early success. This is efficient because it allows rapid progression to definitive investigation of a promising treatment. Many traditional trial designs now incorporate early stopping rules in a more limited way than full adaptive designs, generally using only one or two interim analyses.

An enrichment design allows for the adjustment of inclusion criteria in order to hone in upon patients most likely to benefit from a treatment. In the recent DAWN trial of endovascular therapy for stroke, investigators sought to determine if the Trevo endovascular device could benefit patients presenting outside the therapeutic window for tPA. The investigators thought that discrepancy between the severity of the patient's neurological defects and the volume of the core infarct, quantified by imaging studies and termed the "core mismatch," would be an indicator that the patient had ischemic but still-salvageable brain. They also hypothesized that the size of the core infarct would influence the likelihood of benefit from endovascular intervention, conjecturing that patients with small core infarct sizes would be most likely to benefit. However, it was unknown what maximum core infarct size would define the largest population able to benefit from the intervention. Rather than guess at the best inclusion criteria and ignore the uncertainty, the investigators defined subgroups based on core infarct size. At interim analyses, the adaptive trial design could reduce the largest eligible core infarct size based on observed results and a predefined set of decision rules: if the largest infarct-size subgroup had less than a 40% posterior probability of success, then that group would be excluded from enrollment in later stages of the trial. Adaptive enrichment in this setting protects against the possibility of a failed trial because of inappropriate patient selection based on hypothetical estimates of benefit in patients with different core infarct sizes.

The definition of success for an adaptive trial should closely mirror the primary aims of the trial. In a Phase II adaptive trial, success may be defined as demonstrating a high probability that, if the experimental treatment were tested in a subsequent Phase III trial, the Phase III trial would be successful. Alternatively, success may be defined as a high posterior probability (e.g., >97.5%) of there being a predefined clinically meaningful effect.

When evaluating the effect of adaptive decision rules on the statistical characteristics of a trial, it is best to perform extensive simulations of the proposed trial design. In general, evaluation of simulated trials yields insights into the strengths and weaknesses of the proposed trial design and suggests possible changes to the design. Once these changes are programmed into the adaptive algorithm, the trial may be resimulated to determine if the statistical performance meets the needs of the investigator team. In order to define specified decision rules that are likely to perform well under a variety of circumstances—such as different treatment effects, different dose-response curves, and different rates of adverse events—an adaptive trial is simulated thousands of times under these different "underlying truth" scenarios. As with all trial designs, there are inevitable trade-offs, such as between Type I error and power. Simulation allows these trade-offs to be fully characterized and considered rather than ignored. After simulation, trial parameters, such as the 40% posterior probability rule used in enrichment decisions in the DAWN trial, are selected in light of associated trade-offs. Adaptive decision rules are thus carefully "stress tested" before the first real subject is ever enrolled.

**Adaptive Trials: Disadvantages and Misconceptions**

Although adaptive trial designs have the distinct advantage of being able to account for design parameter uncertainty in a way that traditional trials cannot, they do have limitations and a set of unique challenges. One key limitation of response-adaptive designs is that they require that outcomes (or surrogate markers thereof) are rapidly known relative to the time it takes to complete subject accrual. It would not be feasible, for example, to perform a response-adaptive trial of a therapy for dementia in which all subjects were accrued and randomized within the first year, but outcomes were not known for 20 years. In that case, all subjects would be randomized before any new information was acquired and adaptation could occur. Traumatic hemorrhage is a disease well suited to study with adaptive techniques because patient outcomes are known within a short time frame relative to the duration of the trial.

Another disadvantage of adaptive trials is their more complex design process, which often requires the trial statistician to spend significant effort extensively simulating the trial under various values of trial parameters prior to grant application. This is further complicated by the relative paucity of statisticians who have training in adaptive techniques or extensive experience with them. Funding to support extensive pretrial design is also scarce, with limited availability of "planning" grants that can be used for this purpose.

Even after a rigorous design process, adaptive trials may face unique hurdles in grant review. Uncertainty regarding final sample size may complicate logistical and funding considerations. Reviewers' relative lack of familiarity with adaptive designs carries potential for greater uncertainty in the peer-review process of grant applications and manuscripts.

Despite some true disadvantages of adaptive design, there are also a number of common myths (both positive and negative) about adaptive trials. The first is that adaptive trials are always smaller than comparable fixed trials. In fact, an adaptive trial may be either larger or smaller than a comparable traditional fixed trial design, depending on the true treatment effect of the intervention. If the true treatment effect is larger than initially assumed, the trial will indeed be smaller, but the converse is also true. A smaller-than-expected treatment effect may result in a larger adaptive trial, if the trial is designed to be able to detect that smaller benefit. The outcome that is often avoided by using an adaptive trial design is an inconclusive trial result with "trends toward significance" that leaves investigators without a
clear understanding of a treatment’s efficacy. Given the uncertainty of final adaptive trial size, it is usually necessary to impose “guardrails,” for example, a maximum trial size, in a funding application.

A second group of myths surrounds the regulatory aspects of adaptive trials. Some cite the supposed disadvantages of Bayesian statistics’ lack of popularity and established conventions, referring to regulatory bodies’ general reliance on P values and other frequentist parameters. However, Bayesian statistics are neither a prerequisite for adaptive design nor incompatible with satisfying frequentist requirements. Extensive simulation of trials can be used to ensure that Bayesian designs conform to traditional frequentist requirements, including the control of Type I error rates. Some have argued that regulatory bodies, such as the US Food and Drug Administration, will not accept adaptive designs. However, comments published by the leadership at the US Food and Drug Administration suggest that this is not the case.

A third set of misconceptions exists regarding bias in adaptive trials. The first is that early stopping will substantially bias estimates of the treatment effect. While such bias may result, it is almost always minimal. The second misconception is that adaptive approaches will be highly biased if there are secular trends in patient characteristics. Although secular trends may introduce bias, there are statistical approaches to account for this and to ensure comparison of experimental subjects to contemporaneous controls.

**Platform Trials**

Unlike a traditional clinical trial, which investigates a single treatment for a group of relatively homogenous patients, a platform trial is designed to simultaneously investigate multiple treatments for a disease or a group of closely related diseases. Further, platform trials are often intended to continue beyond the evaluation of the initial set of experimental treatments, with the introduction of new experimental treatments over time.

In the case of remote damage control resuscitation, traumatic hemorrhagic shock encompasses several disease subtypes (e.g., blunt vs. penetrating mechanism, presence vs. absence of concurrent head injury) and also presents a variety of therapeutic targets, for example, approaches to blood product administration, ventilation strategies, and the use of procoagulant medications. This complexity can be daunting with a traditional clinical trial strategy. In order to test three therapies in four different disease subtypes, 12 individual clinical trials would be required (this does not include the testing of combination therapies). A platform trial provides an efficient framework for searching this potentially complex set of therapy-disease subtype combinations to define the best treatment for each patient subtype. A platform trial design can also be used to study treatments that are developed or introduced after the trial has already begun.

The terminology surrounding platform trials is not well standardized and is potentially confusing. The term “basket” trial is often used to describe a trial studying different diseases that share a common feature, such as common mutation in cancers arising from different tissue types. In contrast, an “umbrella” trial studies a single disease with different subtypes, which may be defined by biomarkers. An example would be a trial for breast cancer treatments in which therapies are tested on subgroups defined by positivity for markers such as human epidermal growth factor receptor 2 or estrogen receptor. A platform trial generally investigates both multiple therapies and multiple disease subtypes. In an “open” or “perpetual” platform trial, additional therapies may be added after the trial has begun, whereas a “closed” platform trial cannot accommodate the addition of new therapeutic arms (of note, the number of active arms in an open trial may remain constant over time if new treatments are used only to replace those that have been dropped for futility or demonstrated efficacy). A “master protocol” is a general term for a shared set of administrative, clinical, and research procedures and can be applied to any of the trial types described above. In this article, we will use the term “platform trial” to refer to an open platform trial, unless otherwise specified.

An open platform trial is designed to cycle perpetually through multiple treatments and treatment combinations, searching for the most effective therapeutic strategy. In describing different treatment combinations, it is useful to think of domains (e.g., drugs, classes of drugs, or groups of related treatment options such as blood transfusion targets) within which there are specific treatment choices. Each treatment choice within a domain is called a factor. A factor may be a particular drug dose, a drug choice, or a treatment strategy. When there are multiple domains, any combination of factors across all domains is called a treatment regimen. Finally, we must consider that the optimal treatment strategy may vary by subgroup (Fig. 2). Prominent examples of platform trial designs include the European Prevention of Alzheimer’s Dementia project and the I-SPY 2 trial of neoadjuvant therapies for breast cancer. The inferential approaches used in platform trials may help to simplify a complex range of possible treatment regimens by allowing us to make inferences about factors within treatment domains without testing every possible combination of factors or regimen.

Imagine, for example, a platform trial of resuscitation strategies in traumatic hemorrhagic shock that examines various systolic blood pressure (SBP) resuscitation targets in combination with various tidal volumes for ventilation. If, at some point in the trial, all of the most promising treatment combinations contained a tidal volume of 6 mL/kg ideal body weight, it would not be necessary to test that factor in combination with every possible SBP target. We can infer that this is the superior ventilation strategy and make it the new standard of care for that domain in the trial, even while continuing to randomize patients within the other SBP resuscitation target domain. Traditional trials may attempt to simplify the complex treatment space by introducing “bundles” of therapy (such as in early goal-directed therapy for sepsis), which defines targets in multiple therapeutic domains at once. The downside of this approach is that it is impossible to say, after the trial concludes, which portions of the bundle offer benefit and which may be either ineffective or harmful. In the case of early goal-directed therapy for sepsis, it was eventually shown that several domains of the bundle did not improve mortality.

A platform trial design provides opportunities for increased statistical efficiency through the use of a variety of innovative statistical methods. As discussed earlier, Bayesian adaptation algorithms may improve trial efficiency by increasing subject allocation to the best-performing arms and sometimes dropping poorly performing arms altogether, while allowing a
statistically valid analysis. While Bayesian adaptation algorithms can be used in two-arm trials, the efficiency gains in such trials are smaller than those in a multiple-arm platform trial. Based on a simulation study in which 10% of a large group of virtual treatments for a virtual disease are assumed to be effective, a series of adaptive two-arm trials reduced the number of subjects required to demonstrate the effectiveness of a treatment by 31% compared with a series of traditional two-arm trials. However, an adaptive platform design under the same assumptions reduced the number of subjects required by greater than 50%, while maintaining the same power. This is because open adaptive platforms rapidly cycle through ineffective treatments, allowing new therapies to replace arms that have been dropped for futility. The I-SPY 2 trial is likely the most well-known open platform trial; it has five active treatment arms open simultaneously and has “graduated” two therapies to Phase III testing.

Hierarchical modeling is an analytic method particularly well suited to platform designs because it can increase statistical efficiency by “borrowing” information across patient subgroups, without assuming that treatments are equally effective in all subgroups (as occurs if investigators pool data or assume a common treatment effect) or that treatment effects must be determined in each subgroup in isolation. It is reasonable to assume that the treatment effect observed in one patient subgroup provides some information about likely effects in other subgroups. For example, although patients with hemorrhage due to penetrating trauma and those with hemorrhage due to blunt trauma differ in some respects, one might reasonably guess that a truly effective procoagulant should improve outcomes in both groups, although perhaps not with equal magnitude. A hierarchical model estimates an overall mean treatment effect across subgroups and adjusts estimates of subgroup treatment effects toward this overall mean. This has the advantage of correcting for randomly extreme differences seen in subgroups due to small sample sizes (a forced “regression to the mean”) and increasing the precision of both the overall estimate and the estimates of the treatment effect in each subgroup. The degree of “borrowing” can be dynamically adjusted based on the similarity of observed effects when there are three or more subgroups.

A platform trial provides opportunities to incorporate adaptations, but their use is not prerequisite to achieve gains in statistical efficiency. A “closed” platform trial, basket trial, and umbrella trial may accommodate but do not mandate the use of adaptive techniques. An example might be a trial in which three treatments are independently compared with a shared control group. Fewer control subjects would be needed compared a traditional approach using three separate trials, each with its own group of control subjects. In published simulation studies, this shared control design decreased both the total number of trial subjects and the number of subjects who did not benefit from treatment by 23%. This type of design is already commonly used in Phase II dose-finding studies.

From a logistical perspective, a platform trial design can increase the efficiency of recruitment, administration, and monitoring. A shared screening framework for subjects entering different arms of a platform trial allows for greater efficiency in recruiting potential subjects. For example, a single traditional trial of a SBP target of 80 mm Hg for remote damage control

Figure 2. This figure illustrates the evolution of a hypothetical platform trial over time. At the beginning (Panel 1), patients in both subtypes of disease are randomized between a control standard of care and one of two experimental agents. As the trial progresses (Panel 2), Drug B is found to be insufficiently effective in Disease Subtype 2, and so that arm is terminated for futility. As the trial progresses (Panel 3), a new drug is introduced as an active arm for Disease Subtype 2. As shown in the last panel (Panel 4), a new drug may be introduced for Disease Subtype 1, and combinations of drugs may be allowed as sufficient safety or other data become available.
resuscitation of hemorrhagic shock might exclude subjects with head trauma out of the belief that any benefits of “hypotensive resuscitation” could be mitigated by failure to perfuse an injured brain. If a positive treatment effect is shown, a subsequent trial may examine the effect of the treatment in subjects with concurrent head trauma. In this series of two traditional trials, the screening and exclusion of head-injured subjects from the first trial are a lost opportunity to recruit for the second trial. The alternative platform design with two subgroups—one for subjects with concurrent head injury and one for subjects without it—has the advantage of quickly redirecting subjects who are excluded from one arm into another arm for which they meet eligibility criteria.

A platform trial can and generally should make use of a single governing body or trial steering committee, single data safety monitoring board, and single institutional review board for the investigation of multiple treatments, thereby greatly reducing the labor and cost of trial oversight in comparison to running multiple traditional trials. The Lung-MAP trial of therapies for biomarker-defined subtypes of non–small cell lung cancer is an example of a trial that does not use advanced statistical techniques or a shared control group to gain statistical efficiency but has a unified governance that produces gains in screening and administrative efficiency. Participants are screened for the presence of biomarkers and then enrolled into one of several biomarker-based “substudies,” each of which has a treatment and control arm. The data from each substudy undergo independent statistical analysis.

Example: Adaptive Platform Trial for Remote Damage Control Resuscitation of Hemorrhagic Shock

To understand how an adaptive platform trial might be applied to research questions in the remote damage control resuscitation of hemorrhagic shock, we consider a hypothetical platform trial designed to investigate three domains of resuscitation for hemorrhagic shock across two patient subgroups. The three domains might be the SBP resuscitation target, a target hemoglobin, and a target lactate. Within each domain, specific factors can be tested: hemoglobin resuscitation targets of 7, 8, and 9 mg/dL would each represent three different factors within

Figure 3. This figure shows the possible structure of a platform trial investigating three treatment strategies for patients with hemorrhagic shock. Patients who are enrolled may be randomized to combinations of resuscitation targets, based on SBP, hemoglobin, and lactate level. Data from patients randomized to each combination of these three targets are then collected, analyzed with a statistical model, and then used to preferentially randomize future patients to combinations of targets that are likely to be most effective. In order to understand the statistical performance of a platform trial design, the trial must be simulated under a wide variety of possibilities regarding the characteristics of patients, resuscitation targets, and outcomes (Panel 3). As shown in the last panel, simulated patients may be generated separately for those with different injury characteristics (e.g., penetrating vs. blunt trauma, presence or absence of concomitant head injury), to evaluate the trial’s ability to identify optimal resuscitation targets for patients with different injury patterns.
the hemoglobin domain (Fig. 3A). Additional examples of possible domains include drugs or drug classes, such as a domain comparing of different types hemostatic treatments, for example, tranexamic acid versus a novel hemostatic drug versus a novel hemostatic drug plus tranexamic acid.

In the adaptive design, outcome data will be collected, analyzed according to predetermined statistical models (including Bayesian posterior probability calculations, hierarchical models, etc.) in order to make decisions regarding adaptation at predetermined interim points (Fig. 3B). Patients are then randomized according to the updated allocation scheme. If response-adaptive randomization is used, more patients will be allocated the better-performing arms, and poorly performing arms may be dropped.

Prior to the start of enrollment, the study’s statistician must run trial simulations with virtual patients under a variety of different scenarios assuming some “underlying truth” (Fig. 3C). For example, in one simulated scenario, the best level of hemoglobin may be assumed to be 8 mg/dL, the optimal target SBP may be 80 mm Hg, and the optimal lactate may be 2.0 mmol/L. In the next scenario tested, lactate may be the only domain that influences outcomes, and all factors in the hemoglobin and SBP domains may be equal to control. Although the number of potential scenarios is large, an experienced statistician will select those designed to stress test the variability of trial behavior as well as those scenarios that clinicians deem most clinically plausible. A null scenario, where no factor in any domain improves outcomes over control treatment, must always be included to produce estimates of Type I error, as the Type I error rate generally cannot be determined via analytic methods.

Lastly, after decision cut-points are determined based on simulation and desired operating characteristics, the platform trial can be established to enroll patients with different subtypes of disease, such as blunt and penetrating trauma (Fig. 3D). Depending on the type of trial design, the platform may run perpetually, adding in new arms or agents after it has already begun.

CONCLUSIONS

Although many current adaptive and platform trials are found in fields such as oncology, the potential application of these techniques is much broader. In cancer biology, it is well accepted that a disease such as lung cancer actually encompasses many subtypes of disease, often defined by biomarkers, and also presents many potential therapeutic targets. However, this conceptual framework is equally applicable to traumatic injury, where disease subtypes may be defined by a physiologic parameter, mechanism of injury, or location of resuscitation. There is no less need for investigation of novel therapeutics in traumatic injury than in oncology. Platform trials with the use of adaptive techniques provide an efficient and effective way to investigate the ever-increasing options for the treatment of posttraumatic hemorrhagic shock in remote settings.

DISCLOSURE

R.J.L. is the senior medical scientist at Berry Consultants, LLC, a statistical consulting firm that specializes in the design, implementation, oversight, and interpretation of adaptive and platform clinical trials. Both R.J.L. and his institution are compensated for this work. J.T. declares no conflict of interest.

AUTHORSHIP

J.T. drafted the initial manuscript, and both J.T. and R.J.L. participated in the revision of the manuscript for technical accuracy and language. Both J.T. and R.J.L. take responsibility for the entire content of the publication.

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