



The Real-World Ethics of Adaptive-Design Clinical Trials

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Adaptive-design trials are thought to achieve results more efficiently and treat research subjects more acceptably, but their ethical justification has not yet been adequately explored. It rests on the concept of clinical equipoise—not, as usually thought, on the concept of theoretical equipoise.

Since the mid-twentieth century, randomized controlled trials have grown ubiquitous in medical research, having become the gold-standard method for assessing the efficacy and safety of medical therapies.¹ In an RCT, investigators randomly assign subjects to receive either a new therapy in an experimental arm or an existing therapy in a control arm. Trial participants as well as clinicians carrying out the study are usually blinded to subject assignment. Often, an independent committee monitors an ongoing trial to determine if it must be terminated early due to risks to patients or if one intervention is convincingly superior. These features make RCTs optimal methods for rigorous clinical research. Nevertheless, from the earliest application of modern RCTs in medical research, scientists and observers have deliberated the ethics of randomly allocating study participants to trial control arms. A perennial subject of ethical debate is whether equal

numbers of patients should be randomized to all treatment arms if, as a trial progresses, one arm indicates superior effects. Some critics of traditional RCTs have argued that in such cases, a portion of trial subjects could be unethically randomized to suboptimal treatments.²

Adaptive RCT designs have been proposed as a solution to this concern. Adaptive designs generally involve assessing preliminary results of RCTs at set interim points. The data that have accumulated by these interim points are then used to make alterations to the study design, such as allocating fewer patients to poorer-performing trial arms or dropping inferior arms. Adaptive designs are often perceived as improving trial efficiency. They also have been promoted as ethically advantageous over conventional RCTs because they reduce the allocation of subjects to what appear to be inferior treatments.³ This ethical claim is often used to bolster support for adaptive trials, although it has been the focus of limited bioethical scholarship. Critical assessment of this claim is important, as adaptive designs are changing medical research, with the potential to

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significantly shift how clinical trials are conducted. Policy-makers are swiftly moving to encourage greater use of adaptive designs. In 2016, the newly enacted 21st Century Cures Act instructed the Food and Drug Administration to help product sponsors incorporate adaptive methods into proposed clinical trial protocols and applications for investigational drugs and also biological products.⁴ Adaptive designs have been the topic of much discussion in current clinical research, and although ethics have been part of this discussion, many erroneous ethical arguments circulate about adaptive designs.

In this article, we review the ethical justifications commonly offered for adaptive designs, explore these arguments in the context of actual trials, and contend that clinical equipoise is a useful standard for adaptive-trial ethics. We distinguish between *theoretical* and *clinical equipoise* and explain why ethical arguments related to adaptive trials tend to focus on the former. Theoretical equipoise generally stipulates that randomly allocating patients to different treatment arms in a trial is ethical only if the investigators are completely uncertain which treatment arm is preferable, whereas clinical equipoise allows investigators to randomly allocate patients to treatment arms until treatment outcome differences are sufficiently convincing to reasonably inform the medical community and clinical practice. In adaptive trials, according to theoretical equipoise, adaptively allocating trial patients to the treatment arms that are most likely to be beneficial is ethically optimal. Yet we contend that theoretical equipoise can be an unreliable standard for adaptive ethics, illustrating this argument with examples of historic and contemporary adaptive trials. Researchers and ethicists should prioritize clinical equipoise as a barometer of adaptive-trial ethics. According to clinical equipoise, adaptive trials may assign more subjects to arms deemed likely to be beneficial, but not to the extent that doing so renders the trial

less conclusive or convincing. Clinical equipoise is optimal because it invokes the ability of a study to provide informative data for the research community and considers adaptive-trial ethics in the context of their broader clinical outcomes.

We discuss this ethical approach in light of the current realities of adaptive trials, recommending that policy-makers remain attentive to how ethical goals fit into broader sets of objectives for adaptive trials. Finally, while we contend that clinical equipoise is the most critical principle for the primary ethical concerns posed by adaptive trials, we suggest ethical approaches to deal with some additional concerns unique to adaptive designs.

Theoretical vs. Clinical Equipoise

In 1987, a seminal essay by Benjamin Freedman outlined a new way of thinking about equipoise. Until then, equipoise had been commonly understood as a state of genuine uncertainty among investigators as to which treatment is superior among alternatives tested in a clinical trial. Traditionally, it had been considered ethical for patients to be randomly allocated to trial treatments only as long as equipoise remained regarding the preferred treatment. Freedman contended that this broad understanding of equipoise needed clarification, so he distinguished between two primary interpretations of equipoise: a conventional “theoretical” view and his new “clinical” perspective.⁵

For Freedman, the conventional theoretical interpretation of equipoise demanded that evidence on behalf of different treatments in a trial should be exactly balanced such that investigators have no inclination as to the preferred treatment. According to this definition, when a researcher suspects a treatment is inferior, allocating patients to that treatment is unethical. A trial should end as soon as one treatment appears to be favorable. Freedman identified major problems of unreliability and

instability with this theoretical interpretation of equipoise. Theoretical equipoise can be disrupted when an investigator has any feeling that one treatment arm is superior, requiring the investigator to cease allocating patients to other treatments. Yet there is no standard of evidence that investigators must cite to support their perceptions of treatment effect. Researchers could fully satisfy theoretical equipoise while also being wrong, biased, or premature in drawing conclusions from incomplete data.

To address these concerns, Freedman developed the notion of clinical equipoise, which he defined as existing when there is legitimate professional disagreement within a community of experts as to which treatment is preferable among those tested in a trial. According to clinical equipoise, a trial may generally be continued until sufficient evidence accrues that could reasonably be expected to resolve disagreements within the medical community over preferred treatment options. Whereas theoretical equipoise can be disrupted by the slightest indication of treatment preference, clinical equipoise can be disrupted only by evidence that could reasonably be expected to be convincing to an open-minded and informed medical community. In addition, unlike theoretical equipoise, clinical equipoise permits researchers to assign patients to treatments that are suspected to be inferior if there is genuine uncertainty within the research community as to which treatment option is truly preferable.⁶ Thus, clinical equipoise acknowledges that researchers’ initial suspicions may prove unfounded. It allows for trial designs that can better distinguish actual treatment benefits from spurious and confounded effects. Clinical equipoise also endorses continuing trials long enough to collect necessary data on adverse events caused by experimental treatments. This adverse event information is essential for regulators and prescribers to understand whether or how the

experimental treatment should be put into general practice.

Since Freedman's proposal of clinical equipoise, bioethicists have critiqued and reformulated the concept. For example, critics have pointed out that while clinical equipoise requires satisfying the evidence standards of the clinical community, the clinical community can be misguided or lack full consensus. Standards of evidence for disrupting clinical equipoise can also be vague—medical communities do not always agree about the evidence necessary for a particular trial to be conclusive.⁷ Rather, when considering the amount of evidence necessary to disrupt clinical equipoise, investigators often must rely on their experience and statistical knowledge to determine the quality of evidence that the medical community could be reasonably expected to accept when effectively understanding all trial details.

Despite critiques and reinterpretations, clinical equipoise plays an important role in research ethics.⁸ As one leading source states, clinical equipoise is the ethical justification for beginning an RCT.⁹ Several policy guides for clinical trial ethics include clinical equipoise as an important principle for ethical trial conduct.¹⁰

Clinical Equipoise and Adaptive Designs

Freedman's distinction between theoretical and clinical equipoise is fundamental to the ethics of adaptive designs. Although most ethical arguments promoting adaptive designs are rooted in theoretical equipoise, we suggest that this approach to adaptive-design ethics is inadequate. Instead, policy-makers, regulators, ethicists, and members of industry should rely on clinical equipoise when evaluating adaptive-trial ethics because clinical equipoise takes into consideration a trial's full context and the usefulness of the trial's results for the medical community.

The central difference between adaptive and conventional trials is

that an adaptive trial can use accumulating trial data to alter the study. Prior to commencing an adaptive trial, investigators determine the adaptive method to be used and the conditions under which it should be implemented. They usually establish interim points when a data-monitoring committee will evaluate accruing trial results to determine whether the preset conditions have been met for implementing adaptations.¹¹

What qualifies as an adaptive method is somewhat ambiguous, but there are approximately ten major common adaptive designs.¹² Some established adaptations include dose-finding methods that increase patient allocation to doses that appear more effective and reduce allocation to doses that appear noninforma-

important. Ethical arguments favoring adaptive over conventional trial designs often focus on the possibility that adaptive trials could use interim results to reduce the number of patients receiving what appear to be inferior treatments.¹⁴ These arguments are rooted in theoretical equipoise by focusing on the value of aligning patient allocation with initial perceptions of inferior treatments. When theoretical equipoise is disrupted in an adaptive trial as one treatment appears inferior, fewer patients can be allocated to that treatment, which can be ethically advantageous.¹⁵

Although ethical arguments favoring adaptive designs often move toward prioritizing theoretical equipoise by giving moral meaning to early trial indications rather than to final trial

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tive, dropping treatment groups that seem inferior, adding treatment arms, reestimating the trial sample size, adapting the randomization scheme to increase the odds of assigning patients to a treatment arm that seems to perform well, switching patients from an initial assignment to an alternative treatment, or evaluating initial treatment effects on biomarkers such as specific genetic targets to identify subpopulations who can be allocated to treatment arms according to their genetic profiles.¹³ Adaptive methods vary, but the most common defining feature of adaptive trials is the use of evidence of treatment effects among patients enrolled earlier in a trial to adapt the treatment assignment of patients enrolled later in the trial.

These adaptations are where key distinctions between theoretical and clinical equipoise play out and where, we suggest, establishing clinical equipoise as a standard for evaluating adaptive-trial ethics is

results, this framework entails major problems. In many cases, theoretical equipoise is a helpful but incomplete ethical guide for adaptive methods because altering a trial based on interim results is not necessarily always beneficial. For example, early indications of preferable treatments based on partial results midway through a trial may be inaccurate, negating benefits from adaptive designs. In such cases, ethics scholars have pointed out that adaptive designs will not increase efficient allocation to effective treatments.¹⁶ Further, for trials intended to inform the medical community, advantages of adapting patient allocation following the disruption of theoretical equipoise can be lost if translating the adaptive-trial results into clinical practice is difficult. This problem has occurred among numerous adaptive studies. A trial can move toward satisfying theoretical equipoise by exposing fewer patients to treatments believed to be inferior, but

the benefits of this allocation scheme are undermined if the medical community or a regulatory body requires further studies following the adaptive trial to verify the trial's accuracy. This can ultimately expose more patients to treatments believed to be inferior and can delay rather than expedite the application of trial findings to medical practice. Thus, the perceived ethical advantages of advancing theoretical equipoise with adaptive methods cannot be assumed.

In some cases, theoretical equipoise alone may be a sufficient justification for using adaptive methods. For example, some early-phase trials require only evidence sufficient for researchers to determine which treatment options should be pursued in later-phase trials. If these trials are scientifically sound, aiming to satisfy theoretical equipoise with adaptive methods may be appropriate.¹⁷

However, to be useful, clinical trials usually must be conducted in ways that are transparent and sufficiently informative for the broader medical community. Thus, we suggest that clinical equipoise is often preferable to theoretical equipoise to assess the ethical benefits of adaptive-design trials. Given debates over the limitations of clinical equipoise, we do not contend that clinical equipoise can always be perfectly implemented, nor is it sufficient alone as the guiding principle for the ethics of adaptive trials. Adaptive-design trials, like all studies, involve myriad ethical dimensions, and clinical equipoise must be balanced with other ethical principles outlined in research ethics codes and in significant emerging bioethics scholarship.¹⁸ However, if researchers intend to produce trial data that are as useful as possible, clinical equipoise is a more practical ethical objective than theoretical equipoise because it involves consideration of the full context of an adaptive trial and the reliability of trial results for the medical community when assessing whether adaptations are appropriate.¹⁹

A classic adaptive trial illustrates this point. In 1985, a group

of pediatric researchers planned a prospective randomized study comparing extracorporeal membrane oxygenation (ECMO) versus standard treatment for respiratory failure in infants. Exploratory studies had indicated that ECMO could have therapeutic benefits, and researchers widely believed that ECMO was superior to the existing standard of care. Scientists leading the trial had ethical qualms about using a control arm, since they expected most ECMO patients to survive and most control patients to die. Ultimately, the investigators opted for a “play-the-winner” adaptive randomization method in which each enrolled subject was given a greater likelihood of being randomized to the treatment proven efficacious in the previous patients. The first patient was randomly assigned to ECMO and survived; the second patient was randomly assigned to conventional treatment and died. The following ten patients were assigned to ECMO through adaptive randomization and survived.²⁰ Based on statistical analysis of these twelve patients’ experiences, the researchers concluded that the study proved a higher survival rate for infants on ECMO versus conventional treatment. However, the pediatric research community remained unconvinced, and many clinicians continued to use conventional treatment. Critics of the study found the adaptive method too prone to error, deeming the results insufficient to recommend routine pediatric use of ECMO. They pointed out that the adaptive ECMO trial design led to an unacceptably high likelihood of falsely determining the treatment to be effective.²¹ Two subsequent non-adaptive-design trials had to be organized and conducted, each showing neonatal survival on ECMO superior to conventional treatment, before the superiority of ECMO was more widely accepted.²²

The scientific objective of the original adaptive ECMO trial was to establish the superiority of ECMO for clinical practice. The investigators also sought to make the trial more

ethical by demonstrating the advantages of ECMO quickly and efficiently with as few patients enrolled in the control arm as possible.²³ Since the initial adaptive trial results were unconvincing to the medical community, however, the purported ethical advantages of the efficient trial design were negated, as many neonates continued to receive inferior treatment either as subjects in subsequent trials or as patients receiving conventional treatment. Thus, although the trial authors grounded their ethical argument in theoretical equipoise by claiming it was more ethical to allocate fewer patients to the standard treatment believed to be inferior, no consequential ethical gains were ultimately achieved from the adaptive method. This case study highlights the centrality of interpretability for the ethics of adaptive trials and emphasizes the importance of clinical equipoise as an ethical standard.

Challenges of Interpreting Adaptive Designs

It could be argued that the medical community responded coolly to the adaptive randomization ECMO study in part because of unfamiliarity with the adaptive method, which at the time had not been widely used.²⁴ Since then, more research employing adaptive randomization has been published, although the overall number of such adaptive-design trials is still small, relative to the number of traditional RCTs.²⁵ There also has been substantial discussion of adaptive randomization in the scientific literature,²⁶ and statisticians have worked to make the technique more understandable.²⁷ Experience with adaptive randomization and advances in statistics may render the method more credible today than when the ECMO study was published. Still, questions persist regarding the interpretability of adaptive randomization and many other adaptive methods. These challenges underscore the importance of clinical equipoise as a foundation for adaptive-trial ethics.

The Food and Drug Administration recently categorized most adaptive methods according to whether they are “well-understood” or “less well-understood” from a statistical perspective. Adaptive randomization was described as “less well-understood.” According to the FDA, less well-understood adaptive methods are those with which there has been relatively little regulatory experience and that are not fully understood. The agency noted that less well-understood adaptive designs can cause problems such as falsely detecting a treatment effect, statistical or operational bias in effect estimates, or inconsistency between trial hypotheses and statistical tests. By contrast, the FDA described well-understood adaptive designs as relatively low-risk, well-established methods that may enhance trial efficiency with limited risk of introducing bias or impairing study interpretability.²⁸

The FDA categorizations are useful for clarifying how interpretability plays into the ethics of adaptive-design trials. For example, less well-understood adaptive methods may have posed challenges for trial interpretability, requiring follow-up studies (as occurred in the ECMO study), complicating claims that adaptive methods offer inherent ethical advantages by exposing fewer patients to inferior treatments. To understand the extent to which interpretability challenges may have occurred among extant adaptive studies, we conducted a review of all published adaptive trials in the medical literature and assessed whether the trials used adaptive designs that the FDA has categorized as “well-understood” or “less well-understood.” As search terms for this review, we used various iterations of descriptions of the ten major types of adaptive designs. We excluded phase I trials—the earliest stage of human research, usually conducted in healthy volunteers to test pharmacokinetic and pharmacodynamic outcomes—to focus on phase II, III, and postapproval trials, which are most likely to be used to

inform medical practice or for regulatory approval of experimental drugs and devices. We also excluded trials using adaptive methods that were not universally agreed upon as adaptive by the statistical community. Our search yielded ninety-nine published adaptive trials. We found that since 1978, 80 percent of adaptive studies used methods that the FDA has categorized as “less well-understood.” The majority of adaptive trials of all phases used less well-understood designs.²⁹ As researchers and regulators continue to gain experience with adaptive designs and statisticians persist in efforts to improve the interpretability of adaptive methods, more methods may become well understood.³⁰ Still, given the proliferation

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of less well-understood methods in published adaptive trials thus far, the ECMO scenario is probably not an isolated instance in which interpretability challenges could negate potential ethical gains of adaptive methods. Thus, clinical equipoise ought to be used as a robust benchmark for adaptive-trial ethics. This will ensure that ethical assessments of adaptive trials are as accurate as possible because, to achieve clinical equipoise, researchers must consider optimal patient allocation as well as trial interpretability.³¹

Clinical equipoise as a standard for adaptive-trial ethics does not mean, however, that adaptive designs should be abandoned due to their unfamiliarity. Rather, clinical equipoise would stipulate that in adaptive trials, as in any trials, investigators should collect data that could be reasonably expected to be convincing to an objective and fully informed clinician with accurate understanding of the novel designs.³²

Further Limitations of Theoretical Equipoise

Even when adaptive trials incorporate well-understood methods, theoretical equipoise is not a reliable ethical paradigm. For example, in the basic group sequential design, a common adaptive method, patients are often successively entered into a trial in equally sized groups. Results from each group are evaluated as the study progresses to determine whether it should end or continue to enroll the next group of patients. Investigators set in advance the specific points during the trial when accumulating results will be confidentially evaluated. The FDA has categorized the basic group sequential method as a “well-understood” adaptive design.³³

It is among the least controversial of adaptive methods; indeed, some biostatisticians do not even consider the standard group sequential method to be adaptive.³⁴ But even for a well-understood design such as this, theoretical equipoise can be an insufficient ethical standard.

In June 2012, researchers at study sites throughout the United States initiated a group sequential trial comparing the proposed weight-loss drug combination naltrexone-bupropion (Contrave) against a placebo to assess major adverse cardiovascular events among approximately nine thousand overweight and obese patients with cardiovascular risk factors.³⁵ The trial incorporated preplanned interim analyses in which a data-monitoring committee was to evaluate accumulating results as the study progressed, assessing participant safety and recommending whether to stop or continue the trial.³⁶ The trial used the O’Brien-Fleming group sequential method, which the FDA classifies as

one of the “generally well-understood adaptive designs with valid approaches to implementation.”³⁷ Advocates of the adaptive design declared that it expedited the trial and that the interim results could effectively determine if the drug was safe for public use.³⁸ This argument was rooted in theoretical equipoise by accepting early interim analysis data as sufficient evidence of treatment effects.

By late 2014, after 25 percent of trial results were analyzed, an interim analysis suggested that naltrexone-bupropion reduced risk of cardiovascular death, stroke, and myocardial infarction. Although Orexigen, the pharmaceutical manufacturer sponsoring the trial, had previously agreed not to disclose these interim analysis results, the company shared the data with over 100 individuals, including members of its board of directors. In the spring of 2015, Orexigen filed for a patent covering the apparent cardiovascular benefits of the product, making the 25 percent interim analysis results public, despite having agreed with the FDA to keep such results confidential until study completion. Once 50 percent of study results accumulated and were examined, the trend reversed, and the original positive results were found to be spurious.³⁹ Investigators terminated the study, deeming that the sponsor’s public release of interim analysis results corrupted the study’s scientific integrity. As a result, the contributions of thousands of study participants diminished, as the trial failed to serve its intended purpose of evaluating the drug’s cardiovascular safety.⁴⁰

With respect to theoretical equipoise, the interim analysis results provided investigators with reason to believe that naltrexone-bupropion helps overweight and obese patients at increased risk for adverse cardiovascular events and investigators and sponsors were ethically justified in taking actions accordingly (such as filing for a patent). However, it was misleading to rely on early results. FDA reviewers commented that publicity of the early interim results

undermined the integrity and reliability of the ongoing trial.⁴¹ In addition, since both drugs in the combination product were already available as individual prescriptions, the publicity may have led early-adopter physicians to subject patients outside the trial to the treatment combination based on inaccurate evidence. In this case, it was clearly important for results to continue to accrue and remain confidential before firm conclusions could be drawn and actions taken. This case demonstrates how satisfying theoretical equipoise does not necessarily ethically justify an adaptive design. Had the trial observed patients until sufficient data accumulated without publicly disclosing interim analysis results, it may have satisfied clinical equipoise, with the possibility (but not promise) of ethical gains from an adaptive method.

Adaptive trials can certainly satisfy clinical equipoise. For example, a 1996 phase II trial assessing a combination of vinorelbine and fluorouracil as chemotherapy for advanced breast cancer used a group sequential method enrolling patients sequentially in groups of nine.⁴² The groups were followed and evaluated at interim points, with the possibility for early trial termination with a smaller sample size if the therapy met predetermined thresholds for efficacy. After seven groups had been studied, the treatment demonstrated a sufficient response rate, and the trial was concluded. The authors commented that the method enabled effective and rapid evaluation of the chemotherapy, although they noted that the study did not achieve a “marked reduction in sample size” relative to a conventional trial design.⁴³ They estimated that the adaptive method reduced study sample size by four patients.⁴⁴ Still, the oncology community found the results useful, particularly to inform phase III and subsequent trials, and the study was widely cited in the literature.⁴⁵ The trial satisfied clinical equipoise by providing data that other researchers could effectively interpret. The study also achieved the

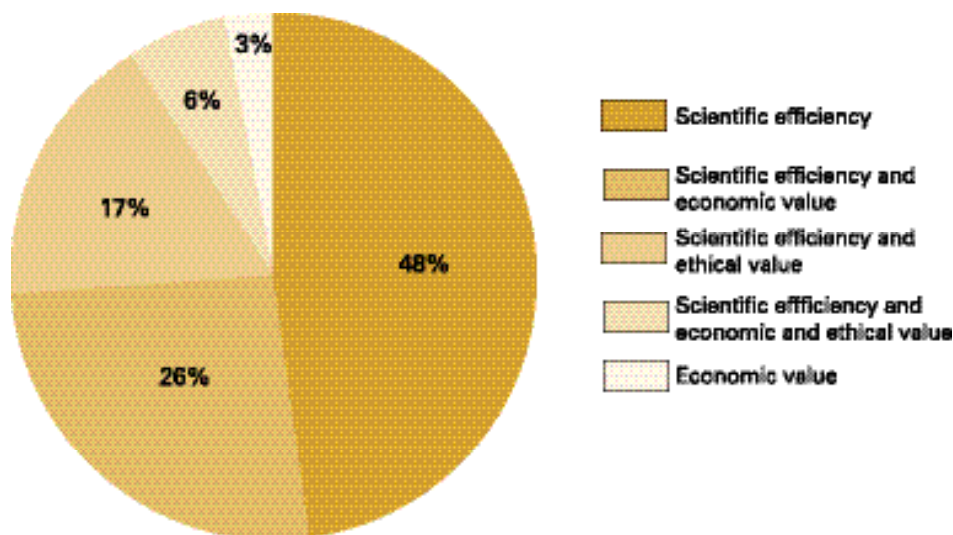
ethical objective of enrolling fewer patients to determine results more efficiently, speeding the process of delivering optimal treatments to cancer patients.

Clinical Equipoise and Adaptive Designs in Emergency Situations

Adaptive designs often have been promoted for their potential to expedite the testing of new treatments in emergency situations.⁴⁶ Efficiency is, of course, often essential and expected in emergency-related research; clinical equipoise is nevertheless still an appropriate standard for emergency-related adaptive trials because interpretability remains important. For example, during the Ebola epidemic in West Africa from 2014 to 2016, it was suggested that adaptive designs could be ethically beneficial by determining effective therapies more efficiently and with minimal allocation of patients to placebo groups. This was a reasonable argument, but adaptive trials in such conditions still must be designed to meet clinical equipoise by providing clear and accurate results to inform practice.⁴⁷ There is no ethical advantage from having an adaptive trial if scientists and clinicians have difficulty interpreting the results and are unable to establish sound evidence-based emergency treatment plans. Further, if treatment plans are implemented based on emerging knowledge that ultimately proves faulty, public trust and willingness to participate in emergency medical response systems can be weakened.

We do not suggest that clinical equipoise standards should burden emergency research. Clinical equipoise potentially can be achieved through briefer studies in emergency settings, as compared with conventional study settings. Continuing a study until meaningful evidence has accrued will lead to different outcomes depending on clinical knowledge needs for the disease at hand. Clinical objectives for some trials

Stated Motives for Using an Adaptive Method in Published Adaptive-Design Clinical Trials



Percentages represent the portion of all published adaptive trials that stated the associated reason(s) for using an adaptive method. Data was drawn from our review of published adaptive trials in the EMBASE, PubMed, Cochrane Registry of Controlled Clinical Trials, and Web of Science databases, yielding ninety-nine trials from 1978 to 2014. This data reflects any statements in the published articles that indicated some form of value of using an adaptive method. "Scientific efficiency" refers to any statements from

article authors indicating that the adaptive method enabled the researchers to come to a scientific conclusion more quickly. "Economic value" refers to any statements indicating financial benefits from using the adaptive method. "Ethical value" refers to any statement that the adaptive method had ethical benefits. Sometimes value statements overlapped, or more than one value statement was included in a trial, as indicated in the chart.

may be straightforward, such as the reduction of mortality without severe side effects. Subtle clinical outcomes may not be part of trial objectives, simplifying the measurements needed from the trial. An adaptive trial may be able to efficiently measure unambiguous critical outcomes in emergency research with sufficient clarity that the medical community deems the adaptive trial to be reliable. In such cases, clinical equipoise would be satisfied. Ultimately, meeting clinical equipoise requires designing a trial to provide sufficient evidence for the specific question under investigation, so it is a flexible standard that can be applied in emergency and nonemergency adaptive trials. Indeed, when an Ebola vaccine was developed, a cluster randomized trial was designed with the well-understood group sequential adaptation

allowing for ending enrollment in the control group due to compelling evidence of vaccine efficacy. The trial enrolled several thousand patients, and when an interim analysis showed a 100 percent vaccine efficacy, allocation of patients to the control group of the trial discontinued. The study continued to measure side effects among enrollees, and questions such as longer-term efficacy are unresolved, but for the trial's intended purpose of proving vaccine safety and efficacy against Ebola in the context of an epidemic, the study effectively informed the clinical community, satisfying clinical equipoise.⁴⁸

Pharmaceutical Trials and Adaptive-Design Ethics

The pharmaceutical industry has played a central role in sponsor-

ing and promoting adaptive trials.⁴⁹ However, ethics and clinical equipoise have not received much attention in published pharmaceutical industry trials. In our review of published adaptive trials, most of which were sponsored by the pharmaceutical industry, we found that authors rarely mentioned ethics of any sort as motivation for using an adaptive method. More often, they suggested scientific or economic motives for deploying adaptive designs, stating that adaptive trials promised to lower research costs and deliver drugs to market faster by reducing trial sample size and shortening trial duration. Overall, it appears that ethical considerations are not a major driving force prompting investigators to use adaptive trials (see the figure). When industry representatives discuss ethics and adaptive trials, they often invoke

theoretical equipoise by arguing that adaptive designs are ethically beneficial because they promise to reduce patient allocation to treatment arms that appear to be inferior. But these claims are often secondary to discussions highlighting the financial benefits of using adaptive methods.⁵⁰

The economic benefits that industry sponsors of clinical trials may accrue through using adaptive designs should not necessarily lead to skepticism of adaptive methods. The goal of economic efficiency is not necessarily unethical; economic interests can potentially align with ethical goals. Yet, bioethicists must understand that industry sponsors of adaptive trials have competing interests when they claim that adaptive designs proffer ethical benefits.

Many bioethicists think the purpose of adaptive designs is to make research more ethical, but this view does not seem to be widely shared outside of bioethics. Some statisticians have argued for an ethical value to adaptive trials or have worked on specific adaptive methods to improve trial ethics by increasing patient allocation to effective treatments while maintaining study power.⁵¹ Yet other scientists have noted that adaptive designs can “provide a false sense of beneficence” by implying a preference to allocate subjects to the better-performing arm, when adaptive trials are actually designed to improve efficiency irrespective of subject welfare, unless attention to subject welfare is explicitly included in the design.⁵² A recent survey of biostatisticians, academic clinicians, and other stakeholders revealed a range of views on adaptive-design ethics, from adaptive designs as definitely ethically advantageous to definitely ethically disadvantageous.⁵³

Understanding that improving the ethics of patient allocation is not the primary driving force behind adaptive trials and that adaptations may not necessarily be ethically beneficial clarifies the role of bioethics in relation to adaptive trials. Adaptive designs should not necessarily be

perceived as tools to increase trial ethics but should instead be seen as novel methods requiring ongoing ethical assessment. Ethicists, institutional review boards (IRBs), and regulatory bodies reviewing adaptive trials have a responsibility to provide practical ethical guidance for adaptive trials, and clinical equipoise can be useful for this task.

Ethics in Implementing Adaptive Designs

The potential benefits of more efficient patient allocation are often the focus of adaptive-trial ethics, and we have described how clinical equipoise is important in determining whether such benefits exist. While equipoise is at the core of adaptive-design ethics, other issues also merit attention, particularly in adaptive-design implementation. For example, concerns have been raised that adaptive trials can be less efficient than standard designs due to the added trial complexities, more complicated planning, lengthened regulatory review of adaptive designs, or some adaptations that reduce efficiency through sample-size enlargement in the pursuit of finding treatment effects.⁵⁴ In addition, prespecified decision rules for trial adaptations can be based on miscalculations of the appropriate threshold for making adaptations, and this can undermine trial integrity and reduce efficiency in the research process.⁵⁵ If adaptive trials are less efficient than conventional trials without providing offsetting benefits, burdening the research development process with the adaptive trial methods is ethically problematic. Therefore, at the outset of adaptive trials, the possibility of ethical drawbacks from reduced efficiency must be carefully weighed against realistic assessments of the likelihood of accomplishing more efficient patient allocation while yielding reliable results.

Adaptive designs also create new responsibilities for data-monitoring committees, the bodies charged with

advising investigators when accumulating trial evidence reaches preplanned thresholds for implementing adaptations. In any trial, a DMC should be independent and without conflicts of interest. However, from an ethical perspective, independence is especially important with adaptive trials, since DMCs directly influence whether and when adaptive designs are implemented. Being free of conflicts of interest when advising on trial design is crucial for a DMC.

Additionally, adaptive methods introduce complexities that can confound the ability of IRBs and trial participants to understand study design, complicating ethical review and informed consent in adaptive trials.⁵⁶ Thus, adaptive-trial IRB protocols and consent forms should be designed with extra care to clearly and effectively convey the trial design and allocation scheme to which patients could be assigned. Trial personnel taking patient consent should be granted extra time to explain the complexities of adaptive designs. Disparities in patient comprehension of adaptive designs might lead patients who understand the scheme to wait to enroll later in a trial, while patients who do not understand the scheme would enroll earlier.⁵⁷ This could make the allocation scheme less fair and could also pose statistical problems by confounding randomization. Thus, to promote trial fairness and integrity, once patients have been informed of trial design, protections should be in place so that they may not inappropriately delay enrollment in adaptive trials.

Studying the Circumstances of Each Trial

Bioethics needs to respond to major new developments in clinical research such as adaptive designs. Although ethical discussions of adaptive designs often focus on theoretical equipoise, this approach has substantial limitations. Theoretical equipoise is often an unreliable ethical benchmark, and it should not be invoked

in a way that overstates the ethical benefits of adaptive designs.

By contrast, clinical equipoise is a more relevant ethical tool, not only because it encourages producing definitive data more likely to be used in general practice, but also because it safeguards trials from preferentially assigning subjects to trial arms wrongly deemed more beneficial due to researcher bias, error, or misleading initial results. We have shown how blanket claims of ethical benefits from adaptive designs can be unhelpful; the ethical value of an adaptive method depends on the specific circumstances of each trial. In some cases, adaptive designs may proffer no ethical benefits, while in other cases, carefully implemented adaptive designs have the potential to offer ethical benefits by reducing the number of patients allocated to less effective trial treatments. Clinical equipoise is an objective that researchers must meet to legitimately claim such ethical benefits.

Clinical equipoise is not a simple paradigm; when conducting a trial using a novel design, researchers cannot know with certainty whether the medical community will find the results interpretable. Investigators must rely on their best judgments as to whether the adaptive designs should be acceptable to adequately informed reviewers. Yet, in a wide range of adaptive-trial scenarios, clinical equipoise has proven to be a helpful foundation for adaptive-trial ethics. Paired with other core principles of research ethics, clinical equipoise can serve as a useful ethical standard for future scientists, regulators, policy-makers, and ethics committees conducting and reviewing adaptive-design trials.

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Notes

1. L. E. Bothwell et al., "Assessing the Gold Standard—Lessons from the History of RCTs," *New England Journal of Medicine* 374, no. 22 (2016): 2175-81.
2. L. E. Bothwell, "The Emergence of the Randomized Controlled Trial: Origins to 1980," PhD diss., Columbia University, 2014, Academic Commons, 138, 172-73.
3. P. Gallo et al., "Adaptive Designs in Clinical Drug Development—An Executive Summary of the PhRMA Working Group," *Journal of Biopharmaceutical Statistics* 16, no. 3 (2006): 275-82; A. B. Antognini and A. Giovagnoli, "Compound Optimal Allocation for Individual and Collective Ethics in Binary Clinical Trials," *Biometrika* 97, no. 4 (2010): 935-46; D. A. Berry, "Bayesian Statistics and the Efficiency and Ethics of Clinical Trials," *Statistical Science* 19, no. 1 (2004): 176-7; C. T. Scott and M. Baker, "Overhauling Clinical Trials," *Nature Biotechnology* 25, no. 3 (2007): 287-92, at 288; P. F. Thall and J. K. Wathen, "Practical Bayesian Adaptive Randomisation in Clinical Trials," *European Journal of Cancer* 43, no. 5 (2007): 862-64.
4. Rules Committee Print 114-67, Text of House Amendment to the Senate, Amendment to H.R. 34, Tsunami Warning, Education, and Research Act of 2015, 114th Cong. (December 2016), 162-63.
5. B. Freedman, "Equipoise and the Ethics of Clinical Research," *New England Journal of Medicine* 317, no. 3 (1987): 141-43; P. B. Miller and C. Weijer, "Rehabilitating Equipoise," *Kennedy Institute of Ethics Journal* 13, no. 2 (2003): 93-118.
6. Freedman, "Equipoise Ethics," 143-44.
7. A. J. London, "Clinical Equipoise: Foundational Requirement or Fundamental Error?," in *Oxford Handbook of Bioethics*, ed. B. Steinbock (Oxford: Oxford University Press, 2009); Miller and Weijer, "Rehabilitating Equipoise"; F. G. Miller and H. Brody, "A Critique of Clinical Equipoise: Therapeutic Misconception in the Ethics of Clinical Trials," *Hastings Center Report* 33, no. 3 (2003): 19-28; P. B. Miller and C. Weijer, "Equipoise and the Duty of Care in Clinical Research: A Philosophical Response to Our Critics," *Journal of Medicine and Philosophy* 32, no. 2 (2007): 117-33.
8. London, "Clinical Equipoise," 572-73; Miller and Brody, "A Critique of Clinical Equipoise," 23-24.
9. C. Grady, "Clinical Trials," in *From Birth to Death and Bench to Clinic: The Hastings Center Bioethics Briefing Book for Journalists, Policymakers, and Campaigns*, ed. M. Crowley (Garrison, NY: The Hastings Center, 2008), 22.
10. Ibid.; The National Bioethics Advisory Commission, *Ethical and Policy Issues in Research Involving Human Participants*,

vol. 1 (Bethesda, MD: National Bioethics Advisory Commission, 2001), 78; Canadian Institutes of Health Research, Natural Sciences and Engineering Research Council of Canada, and Social Sciences and Humanities Research Council of Canada, *Tri-Council Policy Statement: Ethical Conduct for Research Involving Humans* (Ottawa, Ontario, Canada: Secretariat on Responsible Conduct of Research, 2014), 152.

11. Conventional trials can also have data-monitoring committees that evaluate accumulating data to assess whether safety or efficacy thresholds have been met, requiring early trial termination, although conventional trials do not allow for design adaptations.

12. The ten leading types of adaptive-trial designs are adaptive hypothesis, adaptive treatment-switching, biomarker adaptive, adaptive dose-finding, pick-the-winner/drop-the-loser, sample-size reestimation, adaptive randomization, adaptive group sequential, adaptive seamless, and multiple adaptive designs (S.-C. Chow and J.-P. Liu, *Design and Analysis of Clinical Trials*, 3rd ed. [Hoboken, NJ: John Wiley & Sons, 2014], 705-8).

13. S.-C. Chow, "Adaptive Clinical Trial Design," *Annual Review of Medicine* 65, no. 1 (2014): 407-10.

14. R. van der Graaf, K. C. B. Roes, and J. van Delden, "Adaptive Trials in Clinical Research: Scientific and Ethical Issues to Consider," *Journal of the American Medical Association* 307, no. 22 (2012): 2379-80.

15. While theoretical equipoise may not be fully satisfied when certain adaptive methods continue to allocate some patients to apparently less desirable treatment arms, by reducing patient allocation to such arms, adaptive methods can move toward satisfying theoretical equipoise.

16. S. P. Hey and J. Kimmelman, "Are Outcome-Adaptive Allocation Trials Ethical?," *Clinical Trials* 12, no. 2 (2015): 103-04; S. S. Emerson and T. R. Fleming, "Adaptive Methods: Telling 'the Rest of the Story,'" *Journal of Biopharmaceutical Statistics* 20, no. 6 (2010): 1150-65; P. Thall, P. Fox, and J. Wathen, "Statistical Controversies in Clinical Research: Scientific and Ethical Problems with Adaptive Randomization in Comparative Clinical Trials," *Annals of Oncology* 26, no. 8 (2015): 1621-28.

17. The FDA has noted that early-phase exploratory trials may be appropriate scenarios in which for researchers to gain experience with adaptive designs, given that early-phase trials are less likely to need to provide evidence to inform broader clinical practice. Food and Drug Administration Center for Drug Evaluation and Research, Center for Biologics Evaluation and Research, *Guidance for Industry: Adaptive Design Clinical Trials for Drugs and Biologics*

(Draft Guidance) (Silver Spring, MD: U.S. Food and Drug Administration, 2010), 2.

18. World Medical Association, *WMA Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*, 2013, <http://www.wma.net/en/30publications/10policies/b3/>; National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, *The Belmont Report: Ethical Principles and Guidelines for the Protection of Human Subjects of Research* (1979; Washington, D.C.: U.S. Government Printing Office, 1979).

19. Even though the broader medical community may not offer a perfect assessment of the validity of trial results, the process of satisfying the evidence standards of the medical community is less prone to bias than that of satisfying the evidence standards of trial investigators and sponsors. Further, the objective of research usually is not only to provide results that satisfy those involved in a study but rather to establish evidence with broader scientific merit.

20. R. H. Bartlett et al., "Extracorporeal Circulation in Neonatal Respiratory Failure: A Prospective Randomized Study," *Pediatrics* 76, no. 4 (1985): 479-87.

21. J. H. Ware and M. F. Epstein, "Extracorporeal Circulation in Neonatal Respiratory Failure: A Prospective Randomized Study," *Pediatrics* 76, no. 5 (1985): 849-51.

22. Bartlett et al., "Extracorporeal Circulation," 484-86; P. P. O'Rourke et al., "Extracorporeal Membrane Oxygenation and Conventional Medical Therapy in Neonates with Persistent Pulmonary Hypertension of the Newborn: A Prospective Randomized Study," *Pediatrics* 84, no. 6 (1989): 957-63; U.K. Collaborative ECMO Trial Group, "U.K. Collaborative Randomised Trial of Neonatal Extracorporeal Membrane Oxygenation," *Lancet* 348, no. 9020 (1996): 75-82.

23. Bartlett et al., "Extracorporeal Circulation," 480-86.

24. Ware and Epstein, "Extracorporeal Circulation," 849.

25. In a recent separate study reviewing published adaptive trials, we found that eight out of nearly one hundred adaptive trials incorporated adaptive randomization. We conducted a review of all published adaptive phase II, phase II/III, phase III, and phase IV trials in the EMBASE, PubMed, Cochrane Registry of Controlled Clinical Trials, and Web of Science databases through the fall of 2014. We used phrases derived from descriptions of the ten most common forms of adaptive designs. We also included adaptive trial designs found in our review that did not fall into any of the ten common categories of adaptive designs but that fit the FDA's definition for adaptive designs. The date range was open, and the search was conducted in English.

This yielded ninety-nine trials from 1978 to 2014 (please see the figure). We have kept a review manuscript on file. U. S. Food and Drug Administration Center for Drug Evaluation and Research, *Guidance for Industry*, 8-9.

26. E. L. Korn and B. Friedlin, "Outcome-Adaptive Randomization: Is It Useful?," *Journal of Clinical Oncology* 29, no. 6 (2011): 771-76.

27. W. F. Rosenberger, O. Sverdlov, and F. Hu, "Adaptive Randomization for Clinical Trials," *Journal of Biopharmaceutical Statistics* 22, no. 4 (2012): 719-36.

28. The FDA also noted that well-understood adaptive methods either need no statistical corrections related to interim analyses or they adequately account for various trial decisions that could be made based on interim analyses (U. S. Food and Drug Administration Center for Drug Evaluation and Research, *Guidance for Industry*, 7-10, 14-26).

29. The FDA meticulously categorized most adaptive methods as "well-understood" or "less well-understood." The categorization is quite detailed; a single adaptive method could be either well understood or less well understood depending on the circumstances of its implementation, as outlined by the agency (U. S. Food and Drug Administration Center for Drug Evaluation and Research, *Guidance for Industry*, 2, 6, 14-30). Thus, each adaptive trial retrieved in our review was assessed by two reviewers to determine whether the version of the adaptive design used met FDA qualifications for "well-understood" or "less well-understood." The FDA guidance does not deal separately with seamless adaptive trials, so we did not classify seamless trials as either "well understood" or "less well understood." All other adaptive trials were classified. Further details are available in the review manuscript we have on file.

30. Adaptive methods could become more familiar and interpretable; however, statisticians have worked for decades to improve understanding of many adaptive methods, yet numerous core statistical challenges have persisted (S. J. Pocock, "Allocation of Patients to Treatment in Clinical Trials," *Biometrics* 35, no. 1 [1979]: 196; R. Simon, "A Decade of Progress in Statistical Methodology for Clinical Trials," *Statistics in Medicine* 10, no. 12 [1991]: 1795; S. S. Emerson, "Issues in the Use of Adaptive Clinical Trial Designs," *Statistics in Medicine* 25 [2006]: 3270-96).

31. Possibly, less well-understood adaptive methods could be sufficiently reliable to inform the research process without having to be repeated. Such cases could have potential ethical benefits by reducing patient allocation to less preferable treatments. However, such benefits cannot be assumed, rendering clinical equipoise as a

most appropriate ethical standard for adaptive trials.

32. Freedman, "Equipoise Ethics," 144.

33. Group sequential trials can be very similar to conventional trials that have predetermined rules for stopping the trial when efficacy or safety measures have been reached. The distinction is that group sequential trials have preplanned points at which results from succeeding groups of predetermined numbers of patients are evaluated, which is not necessarily the case for conventional trials. Whether the basic group sequential design should be considered adaptive is a subject of debate. However, we follow the FDA guidance, which considers the standard group sequential method to be adaptive. In addition to the FDA, some biostatisticians have described the method as adaptive. U. S. Food and Drug Administration Center for Drug Evaluation and Research, *Guidance for Industry*, 14, 18-19; J. A. Kairalla et al., "Adaptive Trial Designs: A Review of Barriers and Opportunities," *Trials* 13, no. 1 (2012): 3-4.

34. Some authors contrast standard group sequential designs with adaptive group sequential designs; see P. J. Kelly et al., "A Practical Comparison of Group-Sequential and Adaptive Designs," *Journal of Biopharmaceutical Statistics* 15, no. 4 (2005): 719-38.

35. "Cardiovascular Outcomes Study of Naltrexone SR/Bupropion SR in Overweight and Obese Subjects with Cardiovascular Risk Factors (The Light Study)," ClinicalTrials.gov, 2015, at <https://clinicaltrials.gov>.

36. The method fit the definition of a basic group sequential design, as described by the FDA (U.S. Food and Drug Administration Center for Drug Evaluation and Research, *Guidance for Industry*, 14, 18-19); U.S. Department of Health and Human Services, Food and Drug Administration, Center for Drug Evaluation and Research, Office of Translational Sciences, Office of Biostatistics, *Statistical Review and Evaluation: NDA 200063 (Resubmission), Supplement # SDN 42 (eCTD Sequence No. 0041), Naltrexone SR 32 mg/Bupropion SR 360 Mg Tablets*, (2014), 15-19.

37. S. Nissen et al., "Effect of Naltrexone-Bupropion on Major Adverse Cardiovascular Events in Overweight and Obese Patients with Cardiovascular Risk Factors: A Randomized Clinical Trial," *Journal of the American Medical Association* 315, no. 10 (2016): 990-1004, at 993; U. S. Food and Drug Administration Center for Drug Evaluation and Research, *Guidance for Industry*, 18.

38. E. Senchaudhuri, "How to Shorten a Cardiovascular Outcome Trial by Two Years," Cytel (blog), February 10, 2015, at <http://www.cytel.com>.

39. U.S. Department of Health and Human Services, Food and Drug Administration, *Statistical Review and Evaluation*, 15-16; The Cleveland Clinic, "Clinical Trial Testing Safety of Obesity Drug Contrave Halted; 50 Percent Interim Data Released by The Study's Executive Committee," *Cleveland Clinic Newsletter*, May 12, 2015; A. Pollack, "Data Disclosure Leads Researchers to End Study of Obesity Drug," *New York Times*, May 12, 2015; Nissen et al., "Effect of Naltrexone-Bupropion on Major Adverse Cardiovascular Events in Overweight and Obese Patients with Cardiovascular Risk Factors," 990-1004.
40. J. M. Sharfstein and B. M. Psaty, "Evaluation of the Cardiovascular Risk of Naltrexone-Bupropion: A Study Interrupted," *Journal of the American Medical Association* 315, no. 10 (2016): 984-86.
41. U.S. Department of Health and Human Services, Food and Drug Administration, *Statistical Review*, 15.
42. V. Dieras et al., "Efficacy and Tolerance of Vinorelbine and Fluorouracil Combination as First-Line Chemotherapy of Advanced Breast Cancer: Results of a Phase II Study Using a Sequential Group Method," *Journal of Clinical Oncology* 14, no. 12 (1996): 3097-104.
43. *Ibid.*, 3103.
44. *Ibid.*
45. A Google Scholar search reveals that the article was cited seventy-six times as of October 12, 2017. See, for example, H. S. Hochester et al., "Activity and Safety of Vinorelbine Combined with Doxorubicin or Fluorouracil as First-Line Therapy in Advanced Breast Cancer: A Stratified Phase II Study," *Oncologist* 6, no. 3 (2001): 269-77; F. Nolè et al., "Dose-Finding and Pharmacokinetic Study of an All-Oral Combination Regimen of Oral Vinorelbine and Capecitabine for Patients with Metastatic Breast Cancer," *Annals of Oncology* 17, no. 2 (2006): 322-29.
46. S. M. Berry, J. T. Connor, and R. J. Lewis, "The Platform Trial: An Efficient Strategy for Evaluating Multiple Treatments," *Journal of the American Medical Association* 313, no. 16 (2015): 1619-20; E. Cox, L. Borio, and R. Temple, "Evaluating Ebola Therapies—The Case for RCTs," *New England Journal of Medicine* 371, no. 25 (2014): 2350-51; D. Pullman and X. Wang, "Adaptive Designs, Informed Consent, and the Ethics of Research," *Controlled Clinical Trials* 22, no. 3 (2001): 204-09.
47. S. Lanini et al., "Are Adaptive Randomised Trials or Non-randomised Studies the Best Way to Address the Ebola Outbreak in West Africa?," *Lancet Infectious Diseases* 15, no. 6 (2015): 738-45; A. L. Caplan, C. Plunkett, and B. Levin, "Selecting the Right Tool for the Job," *American Journal of Bioethics* 15, no. 4 (2015): 7-9, at 8.
48. Ebola Ça Suffit Ring Vaccination Trial Consortium, "The Ring Vaccination Trial: A Novel Cluster Randomised Controlled Trial Design to Evaluate Vaccine Efficacy and Effectiveness during Outbreaks, with Special Reference to Ebola," *BMJ* 351 (2015): h3740; A. M. Henao-Restrepo et al., "Efficacy and Effectiveness of an rVSV-Vectored Vaccine in Preventing Ebola Virus Disease: Final Results from the Guinea Ring Vaccination, Open-Label, Cluster-Randomised Trial (Ebola Ça Suffit!)," *Lancet* 389, no. 10068 (2016): 505-18; T. W. Geisbert, "First Ebola Virus Vaccine to Protect Human Beings?," *Lancet* 389 (2016): 479-80.
49. L. E. Bothwell et al., "Adaptive Design Clinical Trials in Scientific Literature and Regulatory Evaluation of Drugs by the EMA and FDA: A Narrative Review," unpublished manuscript, last modified October 11, 2017, PDF; Gallo et al., "Adaptive Designs," 275-83; J. Quinlan et al., "Barriers and Opportunities for Implementation of Adaptive Designs in Pharmaceutical Product Development," *Clinical Trials* 7, no. 2 (2010): 167-73.
50. Gallo et al., "Adaptive Designs," 275-82; J. Vollmar, M. Borkowski, and R. Eisebitt, "Top Three Misconceptions of Adaptive Trials," *Applied Clinical Trials* (2008), at <http://www.appliedclinicaltrials-online.com>.
51. J. Hu, H. Zhu, and F. Hu, "A Unified Family of Covariate-Adjusted Response-Adaptive Designs Based on Efficiency and Ethics," *Journal of the American Statistical Association* 110, no. 509 (2015): 357-67.
52. A. M. Lipsky and R. J. Lewis, "Response-Adaptive Decision-Theoretic Trial Design: Operating Characteristics and Ethics," *Statistics in Medicine* 32, no. 21 (2013): 3752-65, at 3763.
53. L. J. Legocki et al., "Clinical Trialist Perspectives on the Ethics of Adaptive Clinical Trials: A Mixed-Methods Analysis," *BMC Medical Ethics* 16, no. 1 (2015): 5-8.
54. S. P. Hey and J. Kimmelman, "Are Outcome-Adaptive Allocation Trials Ethical?," 105; D. L. Bhatt and C. Mehta, "Adaptive Designs for Clinical Trials," *New England Journal of Medicine* 375, no. 1 (2016): 65-74, at 68, 72; T. Cook and D. L. DeMets, "Review of Draft FDA Adaptive Design Guidance," *Journal of Biopharmaceutical Statistics* 20, no. 6 (2010): 1132-1142, at 1138; U. S. Food and Drug Administration Center for Drug Evaluation and Research, *Guidance for Industry*, 24, 33.
55. T. Laage et al., "Ethical Considerations in Adaptive Design Clinical Trials," *Therapeutic Innovation & Regulatory Science* 51, no. 2 (2017): 190-99.
56. Hey and Kimmelman, "Are Outcome-Adaptive Allocation Trials Ethical?," 105; S. B. Saxman, "Ethical Considerations for Outcome-Adaptive Trial Designs: A Clinical Researcher's Perspective," *Bioethics* 29, no. 2 (2015): 59-65, at 64.
57. Van der Graaf, Roes, and Van Delden, "Adaptive Trials," 2379-80.