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Randomized controlled trials in the West African Ebola virus outbreak

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The Ebola virus outbreak in West Africa poses significant global health challenges. It marks the first time in history that the Ebola virus, a level four pathogen, has gained a foothold in a large population for a prolonged period of time. This Ebola virus outbreak has been particularly destructive as it emerged in the context of fractured, barely functioning health systems in societies slowly rebuilding after protracted and violent civil wars. High mortality rates, including the death of a large number of health care professionals, have led to further deterioration in the already poor health status of the affected communities. The economies of the affected nations have suffered. In sum, it is a true humanitarian disaster.

In August of 2014, the World Health Organization (WHO) invoked the International Health Regulations and declared the outbreak a Public Health Emergency of International Concern. Shortly thereafter, in light of rapidly mounting case counts, a complete absence of effective therapy and evidence that clinical and public health countermeasures in place were inadequate to stem the tide of the epidemic, the WHO convened a group to answer the question of whether unregistered interventions should be fast tracked for potential use in the clinical management of Ebola virus. The committee decided unanimously to accelerate research, with the proviso that all efforts be made to evaluate these "in the best possible clinical studies that can be conducted under the circumstances of the epidemic in order to establish their safety and efficacy or to provide evidence to stop their use."[1]

For many, the only path to achieving "interpretable data" is through the use of Randomized Controlled Trials (RCT). In the context of the Ebola virus outbreak, some commentators argue for both the moral and epistemic necessity of RCTs in the context of the evaluation of therapeutic agents.[2,3] These claims are often accompanied by a familiar refrain that RCTs are the "gold standard" for evaluating therapeutic effectiveness.[4] Others have argued that RCTs do not have the epistemic virtues claimed for them and that ethical considerations may make them less than ideal in this setting.[5,6]

In the financial marketplace, the gold standard has long been abandoned as a means to commensurate the value of currencies. In medicine, the time has come to abandon the practice of invoking the "gold standard" label as a defense of RCTs. The convention may serve a rhetorical purpose, but it does not serve in any way as an argument to justify the RCT as a methodology. There are good reasons to question the gold standard rhetoric, and explore the variety of ways in which sound inferences can be drawn in clinical research while addressing ethical concerns. In this article, we will not argue which single study design should be used above all others in the context of an Ebola virus outbreak; rather, we will argue for the kinds of scientific and philosophical considerations that must be brought to the fore.

Questioning the gold standard

In medicine, the gold standard crown is placed on diagnostic tests, therapeutics and research methodologies that are held up as an ideal against which alternatives are to be compared – in research, the double-blind RCT rules. Ironically, the RCT's emerging gold standard status was initially discussed in the medical literature in articles criticizing the new philosophy of methodological monism. The earliest mention of the RCT as gold standard that Jones and Podolsky[7] could locate occurred in a 1982 article by Feinstein and Horwitz in which the authors argued that the scientific gold standard was unattainable and stressed the equal importance of alternatives to the RCT.

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The epistemic ideal in any science should be sound scientific inference, not a particular study design. It is thus worthwhile to revisit the foundations of epidemiological causal inference. To put it simply, in a comparative group study like a clinical trial or cohort study, we can infer that a difference in outcome between groups is causally attributable to a difference in treatment when the groups are otherwise comparable in the right ways. For instance, in Cartwright's "ideal RCT," if the probability of the outcome is higher in the treatment group and all causally relevant factors are distributed identically in treatment and control groups (save for the treatment), then the treatment caused the outcome in the treatment group.[8,9] Comparability is generated through the appropriate selection of comparison groups; and group selection can be made in different ways. One (not infallible) way of creating comparability is to randomly allocate participants to different treatment conditions in a controlled trial.

What are the advantages of using randomization versus other methods of generating comparison groups? Worrall[10] examines several defenses. The first defense is the idealization that randomization balances all confounding causes among trial groups, which may not even be true in probability. Yet, the hyperbole that randomization *guarantees* comparability between trial groups often creeps up in articles defending the use of RCTs, including in the context of Ebola. For instance, Cox et al.[2] claim, "Randomization *ensures* reasonable similarity of the test and control groups" (authors' emphasis). Only in an ideal RCT does this insurance against non-comparability exist. In rebuttal to Worrall, La Caze et al.[11] note that frequentist statistics do not assume that all confounders are balanced. Frequentist statistics are sometimes thought to rely on randomization, but as Worrall[10] argues, this further defense of randomization (if accurate) does not preclude the use of studies utilizing Bayesian statistics. Indeed, many of the adaptive trials proposed to study Ebola virus therapeutics during the outbreak relied on Bayesian analysis.[5]

A third defense of randomization—one that even detractors like Worrall concede—is that it prevents selection bias.[10,11] In a non-randomized study, even if we match comparison groups for all covariates we know about at baseline, we cannot rule out the possibility that selection bias has resulted in a hidden imbalance in a covariate. Once we recognize that all studies (even RCTs) fall short of the guarantee of pristine group comparability and that this ideal is not required anyway, we can ask whether the difference in outcome is large enough to reasonably rule out selection bias. Recall that in their classic advertisement for "large, simple randomized trials," Yusuf et al.[12] argued the need for randomization to rule out selection bias *only when* the expected difference in outcome is small. In the search for an effective treatment to quell the Ebola virus epidemic, investigators were searching for large—not small—treatment effects. Furthermore, selection bias is no threat in the absence of selection. Historically controlled Ebola virus trials, in which the experimental treatment is given to *all* patients at a treatment facility and the control group comprises *all* previous patients at that facility, involves no investigator selection, and the likelihood of large-scale selection bias may be low. All of these subtleties of experimental inference are ignored by the insistence on RCTs simply because they are widely held to be a gold standard.

Was there a missed opportunity?

Given that classical placebo-controlled RCTs are not always epistemically superior, we may have missed an opportunity in the Ebola virus crisis to compare the feasibility and efficiency of different trial designs, identify optimal study designs alongside optimal therapeutic agents, compare therapeutic estimates generated using a variety of trial designs, and—given that no study design is flawless—add robustness to our overall judgments of therapeutic efficacy by basing our judgments on the results of various studies. This, in itself, would have required a certain spirit of inquiry and suspension of epistemological commitments. There was a real possibility to examine how historic controls perform in this context and, arguably, a good case could be made for them here. A variety of adaptive trial designs were also proposed and endorsed by the WHO working group on Ethics and Ebola.[13] The successful implementation of the ring vaccination strategy, although not based on classical randomization, for the Ebola vaccine rVSV-ZEBOV is evidence that alternative trial designs can work.[14] The field of clinical trial design is very dynamic, and immense innovation is taking place across the spectrum from Phase 1–3 trials. Given that science advances through innovation, neglecting important innovations in trial design may hamper progress in the young science of clinical research.

Philosophy of clinical trials

The debate concerning study design in the Ebola virus outbreak serves to remind us of the basic elements of the philosophy and purpose of the clinical trial. That ethical and epistemic considerations need to be balanced in the design of clinical trials is by no means a new idea. Early scholars of the RCT such as A. B. Hill[15] clearly recognized that there was often an inherent trade-off between ethical requirements and scientific rigor. The means to resolving the trade-off came not necessarily through insisting on validity over ethics, but rather in reaching consensus on what is at stake. If a significant reduction in mortality might be gained from an experimental treatment, then health care providers need not be absolutely certain that it is highly

effective before prescribing it; this less than perfect confidence might be achievable through study designs that distribute the potentially life-saving experimental drug to more (or all) trial participants.[15] In other situations, ethical and epistemic considerations may point in the same direction. When an experimental treatment is scarce and it is unclear which patient subgroups can expect the greatest reduction in risk of mortality, randomly allocating the entire treatment stock in a trial setting may be *both* ethically defensible and methodologically sound. As Hill notes, hard thinking is required to achieve this balance regardless.

Part of what was at play in the controversies surrounding trial design to evaluate therapeutics in Ebola virus was a clash of rationalities and perhaps confusion on the questions that the clinical trials were intended to answer. Those championing a humanitarian imperative to provide experimental treatment to as many sufferers as possible were willing to bet that providing some form of therapy that had some biologic plausibility was a worthwhile risk and that study designs that withheld treatment from some patients were deficient given the substantial mortality risk and absence of therapy other than supportive care. Those supporting RCTs place more weight on reducing risk of bias and of confounding our therapeutic knowledge, but as argued, this rationale is not unproblematic.

Perhaps answers to two different questions were being sought by the many different organizations involved in clinical trial research in the Ebola virus outbreak. One question might be as follows: at the conclusion of the outbreak, will the international community be able to say that every avenue was pursued to alleviate the suffering of those afflicted with Ebola virus? The other may be as follows: will the conduct of clinical trials of such-and-such design result in the production of interpretable data such that regulators can approve therapy for future Ebola virus outbreaks? These are very different questions—one recognizing humanitarian aims, one recognizing regulatory aims—and clarity on the questions being asked at the outset may have blunted some (but not all) of the controversies. Closer attention to the philosophy of clinical trials is warranted in the future.

In essence, there is no gold standard study design—the best design depends on purpose and context. In the design of clinical experiments, sound scientific inference and thoughtful ethical deliberation are far better standards to appeal to than gold.

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