Published in final edited form as:

Am J Bioeth. 2015 ; 15(4): 4–10. doi:10.1080/15265161.2015.1010993.

Selecting the Right Tool For the Job

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Abstract

There are competing ethical concerns when it comes to designing any clinical research study. Clinical trials of possible treatments for Ebola virus are no exception. If anything, the competing ethical concerns are exacerbated in trying to find answers to a deadly, rapidly spreading, infectious disease. The primary goal of current research is to identify experimental therapies that can cure Ebola or cure it with reasonable probability in infected individuals. Pursuit of that goal must be methodologically sound, practical and consistent with prevailing norms governing human subjects research. Some maintain that only randomized controlled trials (RCTs) with a placebo or standard-of-care arm can meet these conditions. We maintain that there are alternative trial designs that can do so as well and that sometimes these are preferable to RCTs.

Keywords

adaptive trial design; cluster randomized designs; compassionate access; Ebola treatment trials; elimination of inferior treatments; expanded access; international research; placebo controls; randomized controlled trials (RCT); selection trials; sequential designs; standard of care controls; research ethics

Throughout 2014, Ebola, sadly, evolved from an isolated outbreak in rural Guinea to epidemic status in three nations in West Africa: Guinea, Sierra Leone, and Liberia. Traditional public health responses including isolation and education for containing the epidemic were not rapidly instituted. As a result, these measures were not effective. Public health officials and medical organizations decided to supplement these measures by exploring the efficacy of existing experimental agents including antivirals, prophylactic vaccines, and serum made from the blood of Ebola survivors. These were given to infected health care workers in the United States and Europe outside of any randomized controlled trial. Other organizations began searching for safe and effective therapeutic agents or preventive vaccines that could help stem the tide of the epidemic in West Africa. At the same time, patient groups, ethicists, scientists, doctors, and government officials engaged in an

ongoing debate about the ethics of utilizing experimental agents in affected individuals in hospitals capable of delivering high-quality care, in less capable health facilities in settings in poor areas overwhelmed by the Ebola epidemic, and in areas at most immediate risk of seeing the epidemic spread.

Two distinct positions concerning the kind of trials that should be undertaken emerged: (1) the position of those who advocate the use of “standard of care” or placebo randomized controlled trials (RCTs), widely held to be the “gold standard” in all clinical research (Cox, Borio, and Temple 2014; Joffe 2014; Monti-Masel 2014; Rid and Emanuel 2014); and (2) the position of those who advocate for “alternative” trial designs, a term that covers a range of trial designs from monitored emergency use of unregistered and experimental interventions (MEURI) to cluster randomized controlled trials to selection trials (Adebamowo et al. 2014; Draguez 2014). We believe utilizing a range of trial strategies is the ethical course to take in the midst of an epidemic that has overwhelmed traditional and proven public health responses in poor nations and the capabilities of health care providers working in settings with very limited resources.

The two positions concerning the ethics of trials are not necessarily mutually exclusive. However, some parties advocating randomized trials with placebo controls or with best available standard of care controls maintain that these are the only trials that ought to be undertaken. We and others (World Health Organization [WHO] 2014b) argue that alternative trials are sometimes preferable to such RCTs given the specific challenges present in underresourced environments and the lethal urgency of the Ebola epidemic. Henceforth, we use “RCT” to mean both placebo-controlled and/or standard-of-care-controlled randomized trials, in keeping with current literature. Similarly, “control” here means either of those two types of control arms. This is to carefully distinguish these standard designs from alternative randomized trial designs discussed in the following that offer participants only active interventions.

Part of the reason RCT designs are not morally or methodologically always desirable is that they are not the best design to address the key question being asked. It is important to recognize that the goal of most of the research in West Africa is not to answer the question of whether drug X or biological therapy Y works. It is to quickly figure out what works best. The guiding methodological question of clinical trials at this stage in an epidemic that has spread out of control is not to test a “null hypothesis” that nothing works in carefully controlled circumstances but, rather, to assess among potentially promising agents, some of which have proven safety records, which stands the best chance of working. The wisest use of limited resources is to eschew the null hypothesis and instead to refocus on alternative trial designs that can demonstrate which intervention among those available is most likely to provide benefit to those suffering from Ebola in desperate circumstances. Alternative trials are also responsive to local worries about exploitation, ethical concerns, and practical limits on undertaking canonical RCTs.

Both therapeutic and preventive agents are in or under consideration for testing. Testing the efficacy of novel preventative vaccines raises a unique set of issues. We focus on the ethics of trial design for testing the safety and efficacy of experimental treatments. We also limit

our focus to trials proposed or being undertaken in Sierra Leone, Liberia, Guinea, and other very poor nations or underresourced areas where outbreaks may occur.

PRACTICAL CHALLENGES FOR EFFICACY TRIALS IN POOR NATIONS

Logistical challenges such as poor infrastructure, shortage of health care workers, lack of computers, the need to destroy all materials exposed to infected persons, and treatment units with limited capabilities present serious practical problems for the conduct of any trial. Furthermore, distrust, misunderstanding, and cultural differences permeate many potential study communities (WHO 2014a; 2014b). These practical challenges specific to the West African countries affected have not been adequately addressed by some of the proponents of RCTs.

Perhaps the greatest practical challenge to the use of RCTs in West Africa is that novel agents were administered without RCTs when infected patients were treated in Europe and the United States. Those with Ebola were given a variety of experimental agents along with an evolving series of proven supportive medical interventions meant to maximize survival in spite of Ebola infection. The willingness of health care teams to make rescue a moral priority means that those in West African nations facing Ebola, as well as their leaders, are exceedingly unlikely to accept randomized trials involving placebo arms. They will demand that whatever has been made available for rescue be used to try to rescue infected West Africans in format similar to what was tried in wealthy nations. To do otherwise is to violate the requirement of fairness that like cases ought be treated alike.

Another practical argument against any RCT design is the fact that there are limited quantities of drugs or other agents and poor capabilities for storing them in poor nations. Randomization by itself will not compensate for small numbers when only a tiny supply of experimental drug exists.

There are practical reasons to favor alternative trial designs, such as those that utilize cluster-level randomization. Each study site only needs one set of equipment brought in to get started. Staff can be trained to be proficient in administering one treatment rather than many. All patients get some intervention so they are not receiving treatments different from what is received by others in the same facility.

ETHICAL CONSIDERATIONS

One of the most important and widely acknowledged principles of research ethics says that the possible benefits of a proposed study or clinical trial must outweigh the potential risks to participants. Experimental interventions for Ebola may carry various toxic risks; however, for the infected Ebola patient being treated in resource-limited circumstances, these risks may seem irrelevant or even absurd. Potential risks are outweighed by the obvious benefits to vulnerable individuals, to their communities, and to society at large: alleviating suffering and death among those who have Ebola, and stopping its spread. Researchers will only be able to reap these benefits and discover a treatment for Ebola if clinical trials produce reliable data from which researchers can infer that a given treatment is reasonably safe and

effective. To do so they need good evidence. Thus, the benefits to be gained from research, for example, treatments for Ebola virus, will only be achieved if research is done well.

Some argue that only RCT designs can satisfy the moral requirement of producing benefit (Rid and Emanuel 2014). The thought is that the RCT offers the only reliable route to determining whether an intervention is safe and effective. Some argue that failing to conduct some form of RCT for any Ebola treatment is “a mistake” (Joffe 2014) and “unethical” (Monti-Masel 2014).

In RCTs, half of the trial’s participants are randomly assigned to receive an intervention usually with the best available supportive care even though that may not be very effective, while the other half receives a placebo with supportive care or supportive care alone. Alternatively, participants might be given an “active control” instead of a placebo.

While often trials with “active controls” can use an established efficacious treatment such as aspirin when testing a new analgesic, in the present context “active controls” must be interventions unrelated to what is being studied because there are no established efficacious drug treatments for Ebola yet. Some have suggested using the hepatitis B vaccine as an active control in Ebola drug trials so that participants in the control arm receive some benefit (see Cohen and Kupferschmidt 2014). This strategy seems unlikely to be implemented for a variety of reasons, including chaotic local conditions and cost.

The “gold standard” RCT that its defenders think best is a double-blind RCT, where neither the investigator nor the patient knows who is receiving the experimental intervention and the study is conducted at a prespecified level of statistical significance for testing the null hypothesis. The double-blind RCT reduces bias because investigators cannot skew subject selection by, say, choosing healthier participants for the intervention arm or allowing their hope for a response to cloud their assessment of the results. Randomization with a control group is held to be the best way to minimize other confounding factors in assessing novel interventions:

Without a concurrent randomized control group, individuals who receive the drug will differ systematically from the untreated individuals with whom they are compared. Study participants may be sicker or less ill, younger or older, or identified at earlier or later stages of disease...These differences will confound efforts to reach valid inferences about the safety and efficacy of the drug. (Joffe 2014, 1300)

Defenders of RCTs maintain that failure to have a control group will compromise evidence concerning drug efficacy or safety and produce misleading results making other designs unethical.

How do proponents justify a placebo arm in a trial? In three ways: scarcity, benefit, and a lack of proven efficacy. When there is a scarcity of agents to be tested, the intervention cannot be given to all those who seek it. Randomization to placebo is therefore no worse, and, they argue, ethically more appropriate, than alternative ways of prioritizing access to novel agents such as “first-come first-served,” sickest first, lottery, or ease of delivery.

An additional possible benefit to RCTs is that all participants, whether they've received an intervention or not, will receive close monitoring of their symptoms. Officials of the U.S. Food and Drug Administration have argued that RCTs will not only determine a drug's effectiveness but also deliver improved care to patients in Africa (see Morin 2014).

While the scientific merits of RCTs are powerful, advocates for them have not paid enough attention to competing factors that shape research ethics, such as the need for clinical equipoise in starting an RCT, the weakness of knowledge gained when small sample sizes prevail and available supportive care is given to all, the importance of rapidly finding what agent is best among competitors rather than insisting on starting from scratch as RCTs do, and retaining community trust in participating in any RCT with a control arm. Addressing these concerns is crucially important if any trials are to succeed in very challenging circumstances.

It is widely accepted that randomization is ethical when clinical equipoise is established, that is, when there is genuine uncertainty whether an experimental treatment has benefits or risks that exceed those of conventional care. Equipoise, however, breaks down when available conventional care offers little benefit, some agents appear promising and safe and, mortality is extremely high. This is the case with Ebola in West Africa. Mortality rates where experimental drugs and agents are and will be tested are estimated to be as high as 70% (Hunt 2014). When available conventional care means a high probability of death and a novel intervention holds some possibility of benefit due to promising prior if limited use in humans, animal studies, or simply theoretical plausibility, it is morally problematic to insist on randomizing patients to a control arm in the context of an ineffective standard of care.

Few of us would consent to be randomized when facing utterly lethal circumstances. Where a remotely possible treatment is available for a likely fatal disease, no matter how risky, the sick will almost always opt for it. That is why there has been a push in the United States for compassionate use and expanded access to experimental drugs, devices, and biologics for the terminally ill (Caplan and Moch 2014a). Indeed, since all available agents have been variously deployed against infected persons treated in the United States and Europe, the case for randomization to placebo in West Africa is morally suspect.

The dire reality of Ebola in West Africa is not unique in creating an environment conducive to alternative trials. Research on cancers with poor prognoses as well as other fatal and completely disabling conditions often do not randomize participants for the same ethical reason—a very bleak prognosis. Yet evidence from such studies without placebo control groups is accepted as sufficient for deployment and even for licensing (Bryski 2012). New rules do not need to be created or bent for Ebola research; the regulatory channels to deploy and license drugs tested without RCTs already exist.

A second ethical concern about RCTs is the erosion of trust within the study community occasioned by placebo use. There is ample evidence of mistrust of Western physicians, researchers, military personnel, and government officials both among West Africans during the current outbreak (WHO 2014a; 2014b) and in other resource-poor nations following other disease control efforts, for example, multinational responses to outbreaks of AIDS,

cholera, meningitis, and polio (see Chen 2004; Evans 2011; Harman 2014). While educational efforts have been moderately successful in earning the trust of some communities in Liberia, Guinea, and Sierra Leone, researchers and physicians must continue to cultivate and maintain that trust. Placebo trials using a standard of care that is known to be ineffective will do precisely the opposite. Representatives from communities in West Africa and from Doctors Without Borders have expressed their concern to WHO officials and industry partners that at this point in the epidemic placebo or standard-of-care (SOC) controls based on what is available locally will corrode trust (Cohen and Kupferschmidt 2014; Draguez 2014; WHO 2014a; 2014b). The perception that treatment units are laboratories with the primary aim of producing scientifically valid research rather than hospitals with the primary aim of curing Ebola will not help efforts to encourage admissions to these centers or the needed recruitment to trials. Nor will they build trust for future efforts to study other epidemic diseases in poor communities.

Widespread mistrust raises other moral concerns in that it creates a risk of harm to health care workers and the security of treatment facilities. There is danger of harm to already overwhelmed staff, who may be seen as withholding beneficial treatment, exploiting the desperate by not providing promising drugs, or, mistakenly, as providing agents surreptitiously intended to do harm (Chen 2004). Health care workers have already become victims of intimidation and violence (BBC 2014).

Mistrust might also undermine the integrity of study data. When participants are unsure whether they have received an intervention or placebo, they sometimes share drugs so as to increase likelihood of getting the active agent (Dresser 2014). And it is not clear that overwhelmed health care workers can successfully obtain informed consent or create the controlled environments necessary for sound RCTs. RCTs will not work without community trust, yet implementing them risks eroding that trust.

OBSESSING OVER THE NULL

A pitfall to be especially wary of in debating the merits of RCTs is the “hypothesis testing reflex”—a belief that in any research endeavor one must always test a null hypothesis with adequate control of the type I error rate concerning declaring false positive results. A recent example of the reflex is given by Cox and colleagues (2014). They write:

Scientists at the National Institutes of Health, in collaboration with the Food and Drug Administration, the Biomedical Advanced Research and Development Authority, the Department of Defense, and clinicians caring for patients with EVD in the United States, are leading efforts to develop and implement such trials. They have developed a protocol for an RCT with a BASC [best available supportive care] control group that will use Bayesian analytic methods, allow for the study of more than one investigational drug using a shared control group, and permit incorporation of a therapy into the regimen for the standard-of-care group once it has been shown to be effective against Ebola. (2351)

It is doubtful that this approach would work in West Africa or even the United States. Such a protocol and the attendant required analysis could become so complex that clear and

persuasive evidence would recede behind the Bayesian veil. Such experiments can hardly be replicable, which makes them ethically suspect. Ironically, the Food and Drug Administration (FDA) guidance document on adaptive trial design specifically eschews designs that are not “well-understood” (U.S. Food and Drug Administration 2010).

Cox and colleagues acknowledge but do not elaborate on the practical difficulties such RCTs will face. It is entirely possible that an alternative trial will find an effective treatment. What happens when that treatment is added to the best available supportive care (BASC)? The sample size will be much too small to confer good statistical power for the original BASC comparison, and it will likely be the case that the power for the remaining treatments versus updated BASC comparison will also be very low because the treatment effect sizes may now be much smaller, requiring much larger sample sizes than planned to declare statistical significance with high probability. Statisticians have done their job too effectively if it results in the misconception that every discovery endeavor must test a null hypothesis.

Consider an alternative case akin to some inquiries in West Africa for treating Ebola where testing the null makes no sense. Suppose two schoolyard baseball or cricket team captains are choosing up sides. Testing the null hypothesis that no player is any better than any other player—or worse, testing the null hypothesis that Johnny can’t hit better than a placebo—is the farthest thing from anyone’s mind. The goal is to try to select the best players for your team. Similarly, when one needs to hire an assistant, or to decide on which investment to put in one’s portfolio, or to pick a horse at the racetrack, the testing of null hypotheses as a goal becomes absurd. In all of these cases, what we need is to select the best option or best subset of options in order to move forward. This is the situation in the current lethal Ebola outbreak in West Africa. There is an urgent need to know which among several potential therapies to select to help stop the epidemic.

Defenders of RCTs will point out that if a trial designed to select best treatments does not include a placebo control arm, one will not “know” whether the selected treatment or treatments are any better than those controls. This knowledge is important, but it depends on degrees of evidence rather than an always/never answer. It is well known in cancer and other life-threatening illnesses with no effective treatment that one can and should rely on prior knowledge about the efficacy of standard of care (SOC). With mounting case fatalities in the current epidemic, the usual well-placed concerns about historical controls seem less germane because the information about SOC comes from the here and now. When engineers need to build a bridge across rough waters, they need not test the null hypothesis that the laws of gravity will not operate; they rely on adequately known information, select their materials, and get on with the task.

When only active intervention candidates are included in the randomized trial, a different null hypothesis can be contemplated—that no active intervention is any more or less efficacious than any other one. Assuming it is reasonably plausible that at least some candidates are better than available SOC, if it were actually the case that that null hypothesis were true, we would be happy to select any or all of them, other things like toxic side effects, availability, feasibility, and cost being equal. This is an “indifference zone approach” (Bechhofer 1954).

When selecting among options, we may act with indifference as to which options are selected if they have sufficiently similar efficacy, without seeking to “test” that null hypothesis. If, however, there were a truly superior treatment with a meaningfully large benefit, an experimental design that can identify the correct best candidate or candidates for selection with a prespecified high probability must be used. This is precisely what randomized selection trials offer (Bechhofer et al. 1995; Gibbons et al. 1977; Leu and Levin 2008, Leu et al. 2011). In the current desperate situation, the primary goal of any trial should be selection of the best therapeutics; checking that they are indeed better than SOC may in this case rely on concurrent observational data as an important but secondary goal, because what is sought are winning treatments with large, obvious effects.

Irrespective of the comparison group issue, adaptive trial designs offer appealing features. An adaptive trial is a protocol that allows certain design features to change from an initial specification based on evolving trial information while maintaining statistical, scientific, and ethical integrity. To be scientifically valid, any adaptive trial should be “adaptive by design,” meaning that possible adaptations to the trial protocol are prespecified and made a part of the design itself. This ensures that the trial can be replicated and that adaptations are not made ad hoc (Coffey et al. 2012). It is not always the case that adaptive designs reach answers with fewer subjects than nonadaptive designs, but they do offer statistically valid and ethically appealing options for getting answers to the questions for which answers are being sought.

Suppose there are four candidate treatments. Best expertise thinks one might work better than the other three. If there are multiple treatment centers available, divide them into four groups, one for each treatment. Randomly select one center from each group and enroll one subject from each chosen center to create a quadruplet of subjects, who will each receive one of the candidate treatments. Repeat for the next quadruplet, and so on. If possible, match subjects within quadruplets on major risk factors such as the severity of illness at time of presentation. Keep track of the treatment success tallies, that is, the numbers of cured subjects. Define a prespecified integer, which we will call c here, because it serves as a criterion for both stopping the trial and adaptively eliminating inferior treatments. In this example, we use the criterion $c = 6$.

The procedure is the following. The first time any success tally or tallies trail behind the leading tally by $c = 6$, eliminate that candidate (or those candidates) as inferior, meaning stop randomizing subjects to those treatments. Treatment centers may be switched to other treatments still in the running. Monitoring continues with the remaining treatment candidates at their current tallies. The procedure is iterated until all but one treatment has been eliminated. The trial then selects the remaining one as best.

Such a sequential adaptive selection design can reach a rapid conclusion. In this example, suppose that three candidates might have cure probabilities of 50% each but one might be 75% efficacious. Because the available standard of care might vary between 30% and 50% success, the three candidates might or might not be better than standard of care, but the fourth candidate would be truly superior. Then the preceding procedure will pick the correct winner with probability greater than 99.5% after a total of 104 patients have been

randomized (sometimes more, sometimes fewer, because of the sequential stopping feature). On average, the procedure will incur about 43.5 deaths and 60.5 lifesaving treatments. The first apparently inferior treatment to be eliminated will occur after 64.2 patients have been followed. Toward the end of the trial, patients will be randomized only to the two apparently best treatments. By contrast, a conventional RCT at the 5% two-tailed significance level would require 282 patients to achieve comparable statistical power pitting one active treatment against a placebo control, and more than 500 patients to compare three active treatments against one control.

The key idea behind the efficiency of the selection design is that when one gives up the goal of controlling the rate of type I errors at conventionally small levels, one can select a true winner with many fewer subjects. However, the trial will not commit *any* type I errors if one refrains from declaring any differences “significant” (the holy grail of hypothesis testing). What one has accomplished instead of “significance” is a rapid identification of an apparently best treatment to go forward. If it is obviously better than standard of care, then this is ethically much better.

Of course, even the best designed trial can encounter adverse events once implemented. An independent data safety monitoring committee is especially important in studying high-risk and vulnerable patient populations. Unexpected serious adverse events (SAEs) need to be monitored closely to weigh the risks and benefits of continuing any trial, and those effects need to be communicated to collaborating partners and study participants (Caplan and Zink 2014b). A benefit to the adaptive design feature is that researchers can build into the design the elimination of prospective therapies following certain SAEs. Similar to underperformance on a prespecified criterion, SAEs will constitute a reason to eliminate a prospective treatment from the running. This can be done by allowing SAEs observed within the follow-up period for a given patient to nullify what might otherwise have been tallied as a success on therapy.

Recall that the second leg of the principle of clinical equipoise is to design and conduct a trial in such a way that it has the potential to alter and improve clinical practice. How best to meet that requirement for Ebola trials will be much discussed, but we cannot succeed unless we can assure a sufficient number of subjects will participate in the study. Alternative trial designs with adaptive features, cluster-level randomization, and an adequate array of treatment options within the trial often offer the best chances for success.

CONCLUSION

If the goal of conducting trials in epidemic ravaged West Africa is to rapidly find an intervention that cures the infected and blunts the epidemic, then canonical RCT designs are not the only or even the best choice. The World Health Organization, Doctors without Borders, and other partners who coordinate trials on experimental agents agree (see Boseley 2014). There are practical reasons why placebo or SOC-controlled trials will be difficult if not impossible to undertake. It is particularly important to recognize that testing against the null hypothesis is neither appropriate nor necessary at this point in an out-of-control lethal epidemic. Instituting alternative clinical trial designs can provide useful information for the

elimination or selection of prospective therapies. And that is what morally we owe those who are dying or at grave risk in environments where they have no other realistic means of survival.

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