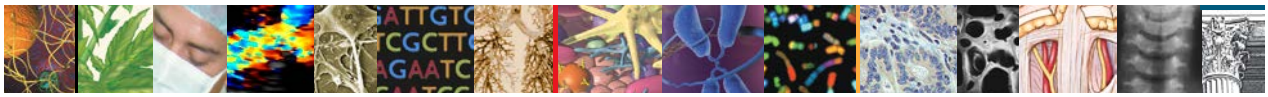

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Perspective

Evaluating Ebola Therapies — The Case for RCTs

Edward Cox, M.D., M.P.H., Luciana Borio, M.D., and Robert Temple, M.D.

The worst Ebola epidemic in history is ongoing. With the number of deaths from Ebola virus disease (EVD) already in the thousands and predicted to rise to tens of thousands,[1] the situation is tragic.

No treatments have yet been shown to be safe and effective in patients with EVD. Some candidate therapies have shown benefit in animal models of infection, and others have shown activity against certain Ebola strains in cell culture, but concerns have been raised about possible toxicity of some of these agents. There is an urgent need to identify therapies that are effective and safe, and well-designed clinical trials are the fastest and most reliable way to achieve that goal.

Studying investigational therapies for EVD presents scientific, practical, and ethical challenges. Not surprisingly, there has been substantial debate about the best and most appropriate study approaches.[2,3] It is generally agreed that a trial with a concurrent control group, in which patients are randomly assigned to receive the test drug plus the best available supportive care (BASC) or to BASC alone, would be the most efficient and reliable way to evaluate the safety and effectiveness of candidate products. Some people in the health care community, however, have argued against such trials, urging instead use of a historical control — that is, making investigational drugs as widely available as their supply allows and then comparing mortality rates among treated patients with rates that would have been expected absent the drugs, on the basis of past experience with EVD. The desire to allow all patients access to investigational drugs is understandable, but there are strong reasons to doubt the ability of such "historically controlled" studies to distinguish effective therapies from ineffective ones.

Insofar as such studies cannot reliably identify effective treatments, their use could have tragic consequences. If historical comparisons falsely suggest a benefit or fail to detect modest but meaningful clinical effectiveness, the investigational drug might be erroneously adopted as effective or discarded as ineffective. Possible consequences include exposure of subsequent patients to harm or to lack of effect from

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the mistakenly adopted treatment and failure to use a drug with a real, though modest, ability to improve survival, as well as failure to further develop an intervention that provides meaningful benefit.

Historically controlled studies compare study outcomes with outcomes in an external group that is thought to be similar to the study participants. The challenge of such trials is identifying a pertinent historical experience. If the two groups are not similar, observed differences in results may be unrelated to the therapy, instead reflecting underlying differences between the groups or differences in supportive care.

Case fatality rates in past outbreaks of EVD have ranged from less than 50% to more than 80%,[4] and even limited supportive care probably improves survival rates. Thus, the historical case fatality rates are irrelevant if current study patients receive better supportive care. Without clear knowledge of the mortality that would be expected with the study's level of supportive care, a historically controlled study cannot determine whether a treatment has helped or harmed patients.[5] In a randomized trial, by contrast, all patients would receive similar supportive care, so that the effect (or lack of effect) of the added treatment could be assessed. Moreover, such a trial could detect even a small but meaningful benefit that a historically controlled trial could not credibly identify.

Randomized, controlled trials (RCTs) with a BASC control group are a powerful tool for evaluating effects of an investigational therapy. Randomization ensures reasonable similarity of the test and control groups and protects against various imbalances and biases that could lead to erroneous conclusions. Properly designed RCTs that give reliable answers are critical to identifying urgently needed treatments for responding to the ongoing Ebola crisis and any future outbreaks.

The number of infected patients greatly exceeds the supply of certain investigational agents. Regardless of debates over trial design or ethics, when there are only limited supplies, most patients cannot receive specific antiviral therapy. RCTs for evaluating these agents will therefore not be depriving patients of treatment but will provide a pathway for identifying effective treatments as rapidly and reliably as possible. Even when sufficient supplies are available, RCTs will provide the definitive answer on effectiveness, in a generally quicker fashion than alternative trial designs.

When preclinical data suggest that a candidate treatment has a low likelihood of clinical effectiveness or may have substantial toxicity, RCTs including a BASC group are the most efficient and reliable way to identify benefits or harm. Given the accelerated development of Ebola drugs (which involves, for example, proceeding on the basis of only limited phase 1 data and little or no traditional phase 2 data) and preliminary data suggesting potential for adverse effects, such drugs need to be evaluated in RCTs with an appropriate control group so that any harm can be detected. Otherwise, it may not be possible to distinguish serious adverse drug effects from manifestations of EVD.

Some public health authorities are reluctant to support RCTs, which they see as traditional and slow trials.[3] However, advances in trial design can and should be incorporated into Ebola RCTs. For example, such trials should include ongoing monitoring of results (e.g., group-sequential designs), adaptive elements, and other trial efficiencies to reduce the time required to identify an effective treatment, particularly a very effective treatment. If one investigational drug clearly shows benefit, trials should incorporate it into the new standard of care for all treatment groups thereafter. Then a regimen adding a different investigational therapy to the new standard of care could be compared with the new standard of care alone. If multiple investigational drugs are simultaneously available for clinical testing, an RCT could include more than one drug and a shared control group. Trials could be designed to assess effects on survival (recovery from disease) as the most important and measurable end point.

RCTs will yield the safety and effectiveness data that are so desperately needed and will do so ethically, giving all patients in a study an equal opportunity to receive the often limited supply of investigational drugs. So far, investigational drugs have generally been used in the few patients treated in the United States or Europe. An RCT with sites in West Africa, the United States, and Europe could result in more equitable distribution, because random allocation provides a fair means of deciding who has access to limited quantities of an investigational drug.

Scientists at the National Institutes of Health, in collaboration with the Food and Drug Administration, the Biomedical Advanced Research and Development Authority, the Department

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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 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. The trial will be initiated first in the United States, with an opportunity for subsequent expansion to affected countries in West Africa. Establishing such trials in those countries is likely to have additional beneficial effects, such as improving supportive care.

Conducting such trials in affected regions will be challenging. It is critical for public health leaders to articulate the rationale for conducting scientifically valid trials, to work closely with local health authorities, and to engage community leaders so that trials can be acceptable to the affected populations. Such efforts are essential if we are to correctly identify therapies that will benefit patients with EVD now and in the future.

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