

Selecting the right tool for the job

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Randomized clinical trials of new drugs have long been considered the "gold standard" in determining safety and efficacy before drugs, biologics, vaccines or devices are introduced to the general public. However, in the case of a deadly, rapidly spreading, infectious disease with no known cure, such as Ebola, ethical considerations demand that reliance only on RCTs be reexamined, according to a new Target Article now online and in print in the *American Journal of Bioethics*.

Authors Arthur Caplan, PhD and Carolyn Plunkett of the Division of Medical Ethics in the Department of Population Health at NYU Langone Medical Center, and Bruce Levin, PhD of Columbia University Mailman School of Public Health, Department of Biostatistics, note in their article that "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 Randomized Clinical Trial 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. There are practical reasons why placebo or Standard of Care (SOC)-controlled trials are difficult if not impossible to undertake."

Dr. Caplan adds, "Local governments and communities will not accept placebo controlled trials in the face of a deadly epidemic especially when there is reason to believe that drugs or other interventions are relatively safe. Nor should they when other trial designs are more appropriate."

The authors further note that there are competing ethical concerns when

it comes to designing any clinical research study - and clinical trials of possible treatments for Ebola virus are no exception. If anything, they conclude, 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," the authors write. "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."

In their article, the authors further point out that the guiding methodologic question of [clinical trials](#) 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 using - a randomized selection" (RS) trial, which has the primary objective of identifying the "best candidate" for the treatment of Ebola or other deadly diseases among competing options.

"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," they state. "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."

"The conventional way of designing randomized clinical treatment trials

in the midst of truly horrific epidemics like the current Ebola Virus Disease outbreak are inadequate," Dr. Levin says. "Researchers have an obligation to do better. We have proposed a design—the randomized selection trial—which addresses the moral responsibility to find promising treatments quickly with a design that respects the needs of those whose lives are at greatest risk."

The article provoked a good deal of accompanying commentary, including from leading figures at the FDA and NIH. The authors respond to these comments hoping that decisions about how best to respond in emergencies with new drugs and agents can secure agreement before the next deadly pandemic.

Provided by New York University School of Medicine

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