Clinical Infectious Diseases

VIEWPOINTS

Rigorous Clinical Trial Design in Public Health Emergencies Is Essential

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(See the Brief Report by Rojek et al on pages 1454–7.)

Randomized clinical trials are the most reliable approaches to evaluating the effects of new treatments and vaccines. During the 2014–2015 West African Ebola epidemic, many argued that such trials were neither ethical nor feasible in an environment of limited health infrastructure and severe disease with a high fatality rate. Consensus among the numerous organizations providing help to the affected areas was never achieved, resulting in fragmented collaboration, delayed study initiation, and ultimately failure to provide definitive evidence on the efficacy of treatments and vaccines. Randomized trials were in fact approved by local ethics boards and initiated, demonstrating that randomized trials, even in such difficult circumstances, are feasible. Improved planning and collaboration among research and humanitarian organizations, and affected communities, in the interepidemic periods are needed to ensure that questions regarding the efficacy of vaccines and treatments can be definitively answered during future public health emergencies.

Keywords. randomized clinical trial; Ebola; ethics.

The West African Ebola outbreak of 2014–2015 was unprecedented. As the first multicountry Ebola epidemic, it affected more individuals and caused more deaths than all previous Ebola outbreaks combined. Unfortunately, awareness of its scope was slow to develop, delaying the initiation of clinical trials. None of the completed therapeutic trials demonstrated efficacy (although the results of 1 study were suggestive); 1 of 4 vaccine trials produced results strongly suggestive of protective efficacy but with interpretive difficulties. To better plan for trials in a future outbreak—whether Ebola or another emerging infection—the US National Academies of Sciences, Engineering, and Medicine convened a committee to systematically review the studies conducted during the outbreak and to make recommendations for the future. The report, released in April 2017 [1], evaluated the study designs proposed/employed [2–9] and considered how to improve the quality of future research. Here we summarize the report's conclusions about study designs.

Randomized controlled trials (RCTs) are generally recognized as the optimal way to evaluate new therapeutic and preventive interventions [10–14]. However, in situations involving serious diseases without satisfactory treatment, this approach has been questioned [15–19]. Although a handful of treatments have been shown to be effective in small, uncontrolled studies, such as platinum for treatment of testicular cancer [20], this is exceedingly rare. Most effective interventions provide modest to moderate improvements, which cannot be reliably identified in uncontrolled studies. The 2 primary attributes of RCTs—use of a concurrent control group and the random assignment of treatments—are critical to drawing valid conclusions about treatment effects.

CONCURRENT CONTROL GROUP

If individuals with a particular disease or condition had uniform outcomes, there would be no need for control groups. But this is rarely the case—even diseases with known poor prognosis typically have variable courses. In addition, emergence of new techniques allowing earlier diagnosis, or, as observed during the West Africa Ebola outbreak, the introduction of improved supportive care over time make the historical experience for evaluating new treatments problematic.

RANDOM TREATMENT ASSIGNMENT

Individuals who agree to participate in a clinical trial may differ from others with the same diagnosis in ways that affect prognosis. Even when adjusting for factors known to affect study outcomes, nonrandomized studies can be misleading due to differences in unmeasured or unknown factors. Countless examples

Received 25 August 2017; editorial decision 6 November 2017; accepted 18 November 2017; published online November 21, 2017.

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Clinical Infectious Diseases® 2018;66(9):1467–9

DOI: 10.1093/cid/cix1032

of purported treatment effects emerging from observational data have been definitively refuted in subsequent RCTs [21–24].

CLINICAL TRIAL DESIGNS DURING THE 2014–2015 EBOLA OUTBREAK

At the outset of the Ebola epidemic, several experimental drugs and vaccines were in very early stages of development and none had yet been studied in humans. Unfortunately, consensus regarding priority interventions and trial designs was difficult to achieve. A particular area of debate was whether an RCT was ethical in the face of such a public health emergency [19, 25]. Some argued that randomization to a placebo control (in addition to all available supportive care) would be unethical given the expected high mortality, and presumed the affected communities would reject such a design. These concerns led several investigative teams to initiate uncontrolled trials of experimental treatments, hoping to observe a survival rate high enough to establish efficacy based on comparison with historical estimates [26–28]. Others suggested initial uncontrolled trials of investigational agents rapidly followed by RCTs for any agent found promising but not definitively effective [3]. This approach was applied to just 1 agent, which did not pass the first stage before the epidemic waned [29]. A "platform" design was also proposed, randomizing individuals among several different treatments and increasing the proportion randomized to treatments that appeared to be more effective as the trial progressed [5]; however, the epidemic was brought under control before it could be implemented. Only 1 RCT, comparing ZMapp to placebo with everyone receiving optimized supportive care, was initiated [30].

Ultimately the uncontrolled therapeutic trials did not demonstrate the extremely large effects required for credible conclusions, and the single RCT evaluating ZMapp did not enroll enough patients before the epidemic waned to definitively assess benefit. The observed mortality of 37% in the control group was substantially lower than the historical rates, demonstrating the difficulty in interpreting uncontrolled data. Had the mortality been as low as 37% in the single-arm trials, the products studied would have been viewed as extremely promising, as expected mortality was at least 50%.

In the case of vaccine trials, randomization was less controversial because the individuals involved were not currently ill. Several RCTs were initiated [31–34], but the only study able to evaluate efficacy used an innovative "ring" strategy in which clusters were defined around observed cases, and then randomized to immediate or delayed vaccination [31]. This approach defined clusters at elevated risk of infection so that despite the waning of the epidemic, enough cases were observed to permit meaningful efficacy analysis. A statistically significant estimate of 100% protection was obtained when individuals in the "immediate" clusters who actually received vaccine (approximately two-thirds of this randomized cohort) were compared to all individuals in the clusters randomized to "delayed" vaccination. However, this analysis violates the intention-to-treat (ITT) principle, which requires inclusion of *all* individuals randomized to both arms whether or not they received the experimental treatment [35]. The ITT results (included as an additional analysis in the final report) yielded a lower estimate of vaccine efficacy of 65%, which did not reach statistical significance. This is not a minor technicality—those randomized to be vaccinated but were not could be different from those who were vaccinated in ways that influenced the likelihood of infection [36]. Moreover, the trial was not masked to control potential biases in identifying cases.

These findings present major challenges for regulators, product manufacturers, and research organizations. Without definitive evidence of efficacy, will products be approved? Will manufacturers ramp up production of the promising products whether or not regulatory approval is granted, in anticipation of "compassionate use" in a future outbreak? Will trial organizers plan further studies using these products as controls instead of using placebo controls?

URGENCY DOES NOT OVERRIDE THE NEED FOR RELIABLE RESULTS

It is understandable that in a context with no known effective therapies, those treating the sick would want to use any accessible and potentially active treatment [37]. But conducting human research in a manner that does not conform to scientific standards and is thus unlikely to yield actionable findings is itself ethically questionable [38]. If drugs were approved based on promising early uncontrolled results, the outcome could be a plethora of new available treatments; individuals and physicians in desperate situations would have multiple drugs to choose from but no reliable information about their effects. No group has understood this dilemma better than the AIDS activists in the late 1980s, who very quickly became strong advocates for rigorous study designs to evaluate new treatments for human immunodeficiency virus infection [39].

Similar considerations apply to vaccines. Public health officials dealing with future outbreaks will face an inevitable and difficult trade-off between obtaining efficacy data as rapidly as possible, and obtaining the long-term observations needed to fully assess product safety and durability of protection.

SUMMARY: PROMOTING FURTHER CONVERSATION AND CONSENSUS

The scientific output from the clinical trials in West Africa has been characterized as "thin" [40]. It took too long for trials to be planned, vetted, and initiated, and as most of the trials were neither randomized nor adequately controlled, results could not in the end support conclusions about safety or efficacy. This experience should motivate investigators to plan for the inevitable future epidemics during the interepidemic periods

and to drive consensus about trial design and conduct among the various research and humanitarian organizations and local communities before the next outbreak, whether of Ebola or another pathogen [41, 42]. Otherwise, we may well repeat the disappointing outcomes of the recent Ebola experience.

Notes

Acknowledgments. The authors acknowledge the invaluable assistance of Patricia Cuff, Michelle Mancher, Emily Busta, Julie Pavlin, and Michael Berrios in collecting and summarizing the information on Ebola treatment and vaccine studies for the National Academies Committee on Clinical Trials during the 2014–2015 Ebola epidemic.

Financial support. This work was supported by the National Academies of Science, Engineering, and Medicine, with funding from the Office of the Assistant Secretary for Preparedness and Response; the US Department of Health and Human Services; the National Institute of Allergy and Infectious Diseases; and the US Food and Drug Administration; the Division of Biostatistics, Epidemiology and Informatics in the University of Pennsylvania Perelman School of Medicine; the Medical Research Council (MRC_UU_12023/23); and the Boston University Schools of Medicine and Public Health.

Potential conflicts of interest. C. D. W. is an employee of Sanofi, Inc. A. G. B. has received grant funding from the UK Medical Research Council. J. D. L. has received grant funding from the Danish National Research Federation. K. M. E. has received grant funding from Novartis for unrelated research. S. S. E. served on a data monitoring committee for GeneOne and as an investigator on a study for which drugs were provided by AbbVie. All other authors report no potential conflicts. All authors have submitted the ICMJE Form for Disclosure of Potential Conflicts of Interest. Conflicts that the editors consider relevant to the content of the manuscript have been disclosed.

References

1. National Academies of Science, Engineering, and Medicine. Integrating clinical research into epidemic response: the Ebola experience. Washington, DC: National Academies Press, 2017. Available at: https://doi.org/10.17226/24739. Accessed 12 May 2017.
2. Caplan AL, Plunkett C, Levin B. Selecting the right tool for the job. Am J Bioeth **2015**; 15:4–10.
3. Whitehead J, Olliaro P, Lang T, Horby P. Trial design for evaluating novel treatments during an outbreak of an infectious disease. Clin Trials **2016**; 13:31–8.
4. Proschan MA, Dodd LE, Price D. Statistical considerations for a trial of Ebola virus disease therapeutics. Clin Trials **2016**; 13:39–48.
5. Berry SM, Petzold EA, Dull P, et al. A response adaptive randomization platform trial for efficient evaluation of Ebola virus treatments: a model for pandemic response. Clin Trials **2016**; 13:22–30.
6. Richardson T, Johnston AM, Draper H. A systematic review of Ebola treatment trials to assess the extent to which they adhere to ethical guidelines. PLoS One **2017**; 12:e0168975.
7. Doussau A, Grady C. Deciphering assumptions about stepped wedge designs: the case of Ebola vaccine research. J Med Ethics **2016**; 42:797–804.
8. Rid A, Miller FG. Ethical rationale for the Ebola "ring vaccination" trial design. Am J Public Health **2016**; 106:432–5.
9. Lipsitch M, Eyal N. Improving vaccine trials in infectious disease emergencies. Science **2017**; 357:153–6.
10. Hill AB. The clinical trial. N Engl J Med **1952**; 247:113–9.
11. Byar DP, Simon RM, Friedewald WT, et al. Randomized clinical trials. Perspectives on some recent ideas. N Engl J Med **1976**; 295:74–80.
12. Sacks H, Chalmers TC, Smith H Jr. Randomized versus historical controls for clinical trials. Am J Med **1982**; 72:233–40.
13. Armitage P. The role of randomization in clinical trials. Stat Med **1982**; 1:345–52.
14. Bothwell LE, Podolsky SH. The emergence of the randomized, controlled trial. N Engl J Med **2016**; 375:501–4.
15. Hellman S, Hellman DS. Of mice but not men. Problems of the randomized clinical trial. N Engl J Med **1991**; 324:1585–9.
16. Gehan EA, Freireich EJ. Non-randomized controls in cancer clinical trials. N Engl J Med **1974**; 290:198–203.
17. Hellman S. Randomized clinical trials and the doctor-patient relationship: an ethical dilemma. Cancer Clin Trials **1979**; 2:189–93.
18. Schuklenk U. Drug testing and approval in cases of people with catastrophic illness: ethical issues. Clin Res Regul Affairs **1998**; 15:145–57.
19. Adebamowo C, Bah-Sow O, Binka F, et al. Randomised controlled trials for Ebola: practical and ethical issues. Lancet **2014**; 384:1423–4.
20. Einhorn LH, Williams SD. The role of cis-platinum in solid-tumor therapy. N Engl J Med **1979**; 300:289–91.
21. Rossouw JE, Anderson GL, Prentice RL, et al; Writing Group for the Women's Health Initiative Investigators. Risks and benefits of estrogen plus progestin in healthy postmenopausal women: principal results from the Women's Health Initiative randomized controlled trial. JAMA **2002**; 288:321–33.
22. Echt DS, Liebson PR, Mitchell LB, et al. Mortality and morbidity in patients receiving encainide, flecainide, or placebo. The Cardiac Arrhythmia Suppression Trial. N Eng J Med **1990**; 324:781–8.
23. Stadtmauer EA, O'Neill A, Goldstein LJ, et al. Conventional-dose chemotherapy compared with high-dose chemotherapy plus autologous hematopoietic stem-cell transplantation for metastatic breast cancer. Philadelphia Bone Marrow Transplant Group. N Engl J Med **2000**; 342:1069–76.
24. Omenn GS, Goodman GE, Thornquist MD, et al. Effects of a combination of beta carotene and vitamin A on lung cancer and cardiovascular disease. N Engl J Med **1996**; 334:1150–5.
25. Fleming TR, Ellenberg SS. Evaluating interventions for Ebola: the need for randomized trials. Clin Trials **2016**; 13:6–9.
26. van Griensven J, Edwards T, de Lamballerie X, et al; Ebola-Tx Consortium. Evaluation of convalescent plasma for Ebola virus disease in Guinea. N Engl J Med **2016**; 374:33–42.
27. Sissoko D, Laouenan C, Folkesson E, et al. Experimental treatment with favipiravir for Ebola virus disease (the JIKI Trial): a historically controlled, single-arm proof-of-concept trial in Guinea. PLoS Med **2016**; 13:e1001967.
28. Dunning J, Kennedy SB, Antierans A, et al. Experimental treatment of Ebola virus disease with brincidofovir. PLoS One **2016**;11:e0162199.
29. Dunning J, Sahr F, Rojek A, et al; RAPIDE-TKM Trial Team. Experimental treatment of Ebola virus disease with TKM-130803: a single-arm phase 2 clinical trial. PLoS Med **2016**; 13:e1001997.
30. Davey RT Jr, Dodd L, Proschan MA, et al; PREVAIL II Writing Group; Multi-National PREVAIL II Study Team. A randomized controlled trial of ZMAPP for Ebola virus infection. N Eng J Med **2016**; 375:1448–56.
31. Henao-Restrepo AM, Camacho A, Longini IM, 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 **2017**; 389:505–18.
32. Kennedy SB, Bolay F, Kieh M, et al; PREVAIL I Study Group. Phase 2 placebo-controlled trial of two vaccines to prevent Ebola in Liberia. N Engl J Med **2017**; 377:1438–47.
33. Widdowson MA, Schrag SJ, Carter RJ, et al. Implementing an Ebola vaccine study—Sierra Leone. MMWR Suppl **2016**; 65:98–106.
34. Winslow RL, Milligan ID, Voysey M, et al. Immune responses to novel adenovirus type 26 and modified vaccinia virus Ankara-vectored Ebola vaccines at 1 year. JAMA **2017**; 317:1075–7.
35. Detry MA, Lewis RJ. The intention-to-treat principle: how to assess the true effect of choosing a medical treatment. JAMA **2014**; 312:85–6.
36. Horne AD, Lachenbruch PA, Goldenthal KL. Intent-to-treat analysis and preventive vaccine efficacy. Vaccine **2000**; 19:319–26.
37. Jacobson PD, Parmet WE. A new era of unapproved drugs: the case of Abigail Alliance v Von Eschenbach. JAMA **2007**; 297:205–8.
38. Emanuel EJ, Wendler D, Grady C. What makes clinical research ethical? JAMA **2000**; 283:2701–11.
39. Gonsalves G, Zuckerman D. Commentary: will 20th century patient safeguards be reversed in the 21st century? BMJ **2015**; 350:h1500.
40. Cohen J, Enserink M. Infectious disease. As Ebola epidemic draws to a close, a thin scientific harvest. Science **2016**; 351:12–3.
41. Pigott DM, Deshpande A, Letourneau I, et al. Local, national, and regional viral haemorrhagic fever pandemic potential in Africa: a multistage analysis. Lancet **2017**. doi:10.1016/S0140-6736(17)32092-5.
42. Dzau V, Fuster V, Frazer J, Snair M. Investing in global health for our future. N Engl J Med **2017**; 377:1292–6.