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Evaluating interventions for Ebola: The need for randomized trials

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Addressing challenges created by infection with Ebola virus

The Ebola outbreak in West Africa in 2014 increased recognition of the need for effective and safe interventions for the prevention and treatment of the severe and often fatal illness caused by infection with Ebola virus. Randomized clinical trials, preferably conducted in a blinded manner, provide the most reliable insights about the benefits and risks of strategies to reduce the clinical burden of Ebola-related illness.

Utility of historically controlled versus randomized controlled trials

Medical interventions must be evaluated in a manner that is ethically acceptable, efficient, and reliable.¹ Ethical considerations relate to safeguarding the interests of study participants, and to achieving timely and reliable insights about interventions to enhance the health of the public. While we strive to achieve efficiency by reducing financial costs, number of participants, burdens on medical personnel and study duration, these efforts should not lead to diminished reliability; the goal of clinical research is not simply to provide those pursuing safe and effective interventions a “choice,” but rather an “informed choice.”

An apparently efficient approach uses an existing cohort that had received ‘standard-of-care’ as the comparator for a prospective cohort that would be provided an experimental intervention. There are two well-recognized concerns with this “historical controls” approach. The first is our inability to ensure that all important prognostic covariates, even those not measured (or even unknown) are balanced across intervention groups. While statistical adjustments can be made in an attempt to address imbalances, known and recorded covariates capture only the “tip of the iceberg,” since most factors explaining these imbalances are unrecognized or unrecorded, i.e., are “below the water line.” The second is

the (often very real) possibility that supportive care and other concomitant diagnostic and therapeutic interventions have improved outcomes over time, independent of the treatments to be compared.

Pocock² proposed several conditions that improve the scientific acceptability of using historical controls, by identifying circumstances closer to what is provided by randomization. Relative to the experimental group, the historical control group should have received the same background standard treatment; it should have been part of a recent clinical trial containing the same requirements for patient eligibility; it should have a similar distribution of important patient characteristics; and it should have the same methods of treatment evaluation. Furthermore, there should be no other indications leading one to expect differing results.

While it is unlikely that historical controls would satisfy all these conditions, their use could be justified when exceptions are modest, especially, as stated by Byar et al,³ if there is “*a justifiable expectation that the potential benefit to the patient will be sufficiently large to make interpretation of the results of a nonrandomized trial unambiguous.*” We briefly consider two such settings: primary biliary cirrhosis (PBC) and pneumonia.

Many considered liver transplantation to be an effective option for PBC patients, after the emergence of immunosuppressive treatments that radically reduced the risk of organ rejection. To assess its efficacy using historical controls, the survival of a cohort of 161 consecutive PBC patients receiving liver transplantation, performed by Starzl and colleagues in the early 1980s, was compared with that of an historical control of 312 PBC patients from Mayo Clinic. These control patients had been enrolled during 1974-1984 in placebo-controlled clinical trials of D-penicillamine, consistent with a Pocock criterion. The entire Mayo cohort was considered an acceptable standard-of-care control because that drug had no effect on survival. Comparing outcomes adjusting for several prognostic factors showed that liver transplantation provided an estimated 75% relative reduction in death rate: two-year mortality was 69% in the Mayo cohort versus 26% in the transplantation cohort.⁴⁻⁶

The second example arises from studies of sulfonamides and penicillin in the pneumococcal pneumonia setting in the late 1930s, soon after R.A. Fisher introduced the concept of randomization but before its routine implementation in clinical research. An overview of 16 articles provided evidence from nearly 7000 pneumonia patients assigned one of these antimicrobials or a ‘no specific treatment’ standard-of-care.⁷ This historical control appeared to be free of substantive violations of the Pocock conditions. After adjusting for two strongly prognostic factors, patient age and bacteremia status, the evidence revealed that these antimicrobials reduced the odds of mortality by a factor of 5. For example, in non-bacteremic subjects above 50 years of age, 50% mortality was reduced to 16%. (So yes, it's true we didn't need RCTs to evaluate penicillin!)

While these illustrations suggest that historical controls can have utility when experimental regimens truly provide extreme benefit, caution is needed if moderate or even large estimated effects are obtained from historically controlled evaluations conducted in a manner allowing risks of substantial confounding. The work of Nobel Laureate Linus

Pauling and colleagues, who conducted historically controlled evaluations of mega-doses of Vitamin C in pre-terminal cancer patients, is a classic example. After publishing an estimated 50 vs. 210 day difference in median survival,⁸ further selective culling of the experimental and control groups resulted in a second publication reporting an even greater benefit.⁹ However, subsequent evaluations of this regimen in a placebo-controlled randomized trial revealed the treatment had no survival benefit.¹⁰

Historical controls have limited utility in evaluating medical treatments because true effects of interventions are much more likely to be modest to moderate than extreme. When benefits are meaningful but modest, uncontrolled confounders can readily lead to misleading conclusions. The landmark Women's Health Initiative¹¹ revealed that post-menopausal hormone supplementation provided an adverse rather than beneficial effect on cardiovascular risks, in clear contradiction to findings from many prior carefully conducted historically controlled studies.

Randomization eliminates systematically occurring imbalances for covariates either above or below the water line. While randomly occurring imbalances can arise, these too diminish as sample sizes increase, and can be mitigated by stratification for important prognostic factors. Additional considerations motivate the use of randomized trials. By being inherently prospective, these trials avoid an important risk of bias, present in the historically controlled setting as seen in the publications by Pauling and colleagues, when selection of membership in the control cohort can be influenced by knowledge of outcome. Furthermore, when using randomized rather than historical controls, it is more achievable to maintain confidentiality of interim data. Considerable experience establishes the importance of such confidentiality in avoiding prejudgment and protecting trial integrity.¹²⁻¹⁴

Some recent experiences illustrate concerns about prejudgment of interim data in Ebola trials. The public release of interim data from the JIKI historically controlled evaluation of favipiravir in Ebola-infected patients allowed over-interpretation of evidence from the initial 69 patients due to lack of adjustment for major confounders as well as for multiplicity arising from the conduct of analyses over time and within post-hoc subgroups.¹⁵⁻¹⁷ In a second illustration, the interim results from the open label randomized rVSV-ZEBOV vaccine trial appear to have been reported when even the per-protocol analysis had not crossed the pre-specified monitoring boundary.¹⁸ Of further import is the concern that the per protocol analysis, given primary attention in the interim analysis of this vaccine trial, may meaningfully violate the integrity of the randomization. In that analysis, all randomized individuals who were 'eligible' (i.e., being at least 18 years of age and not pregnant or breastfeeding) were included in the delayed vaccine control arm, yet the authors excluded one-third of these 'eligible' randomized individuals from the immediate vaccine arm because they did not consent to the vaccination. In settings where randomization is conducted prior to obtaining consent as in the rVSV-ZEBOV trial, the intention-to-treat analysis that includes all eligible randomized individuals in both arms may attenuate the estimate of vaccine efficacy, but excluding a large subgroup in the experimental arm because they did not consent to receiving the experimental intervention raises the important concern of artificially overestimating the strength of evidence for efficacy, potentially leading to concluding benefit for an ineffective intervention. While randomization provides

important methodology in the quest to reduce risks of bias, it also is of importance to preserve the integrity of randomization by conducting trials in a manner that reduces the risk of missing data and by using intention-to-treat analyses to prevent bias.¹⁹

Addressing a prerequisite of ethical research

Clinical trials, particularly when conducted in developing countries such as those experiencing recent Ebola outbreaks, should address the ethical prerequisite that these trials be designed to provide evidence relevant to the setting where they are conducted.²⁰ Hence, the control subjects should receive a regimen that, during the trial or at its completion, would be a version of standard-of-care in that setting. For illustration, the HIVNET 012 trial evaluated a 'single dose' nevirapine regimen as a safe, affordable and feasible approach in developing country settings for prevention of mother-to-child transmission of HIV.²¹ In that trial, conducted in Uganda, the control regimen was based on short course zidovudine rather than the standard triple drug therapy used in developed countries but not in Uganda. HIVNET 012 established that nevirapine provided an approximate relative 40% reduction in risk of mother-to-child transmission, a result that considerably influenced strategies used to effectively prevent spread of HIV in Uganda and similar settings. In contrast, the ACTG 316 trial conducted in developed countries provided all mothers background triple drug therapy, while randomly adding either nevirapine or placebo. This trial, providing results relevant in developed but not in developing countries, established that nevirapine did not provide added benefit when delivered in that manner.²² Had HIVNET 012 used the same regimens, nevirapine would not have been recognized as effective and adopted, and tens of thousands more infants would have been HIV-infected.

Some conclusions regarding the Ebola setting

In current settings in which trials to treat or prevent Ebola virus infections would be conducted, it is very improbable that historical controls would adequately satisfy the Pocock conditions. The case-fatality rate (CFR) for Ebola virus disease has ranged widely not only across regions²³ but also across time. Within Sierra Leone, the CFR declined during 2014 from 74% to 23%,²⁴⁻²⁵ (see Table 1). In remote rural areas of Liberia during 2014, the *"overall CFR declined significantly over time ($p=0.002$), from 92% in August and September to 60% in December"*.²⁶ Subject factors, such as viral species, viral load, and time since infection can be strongly prognostic, as can be the quality of medical care, such as the ability to diagnose and correct severe metabolic derangements and, of particular importance, the provision of full hemodynamic support in the form of aggressive fluid replacement. Although some of these factors are known and thus could be included as covariates in comparisons with historical controls, it is very likely that that rapid and continuing changes in such factors as supportive care and viral species would severely undermine the validity both of historically controlled studies and, notably, of naively analyzed trials using response-adaptive randomization.

In current clinical settings where prognosis post-infection with Ebola virus is rapidly changing, randomized trials greatly reduce the risk of erroneous conclusions. While false negative conclusions could lead to abandoning lifesaving interventions, false positive

conclusions are at least as problematic since they could result in the use of ineffective treatments. As Chief Justice Thurgood Marshall argued ²⁷ in the setting of the laetrile debate, “*An otherwise harmless drug can be dangerous to any patient if it does not produce its purported therapeutic effect... if an individual suffering from a potentially fatal disease rejects conventional therapy in favor of a drug with no demonstrable curative properties, the consequences can be irreversible*”

Settings such as meningococemia in infants, pancreas cancer, severe sepsis and HIV provide a wide precedent for the conduct of randomized trials that are both ethical and feasible, even when addressing life-threatening diseases. When confronting such diseases, the need is particularly compelling for timely AND reliable evidence about safety and efficacy of experimental interventions. The urgency of the need must not lead to the rushing out of treatment strategies that may be ineffective or even harmful. Randomized clinical trials, designed with appropriate monitoring and the possibility of early termination if interim results are persuasive, provide an ethically motivated approach to optimally inform strategies to reduce the clinical burden of Ebola-related illness.

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Table 1
Mortality Statistics during 2014 in Sierra Leone

<u>Date</u>	<u>Sample Size</u>	<u>Site</u>	<u>Mortality</u>
May-June, 2014 ²⁴	106	Kenema, Sierra Leone	74%
Sept.-Oct. 2014 ²⁵	151	Freetown, Sierra Leone	48%
Oct.-Nov., 2014 ²⁵	126	Freetown, Sierra Leone	32%
Nov.-Dec., 2014 ²⁵	304	Freetown, Sierra Leone	23%