Randomised controlled trials for Ebola: practical and ethical issues

2 months ago, when the numbers known to have died from Ebola in west Africa could still be counted in hundreds, WHO made an important statement about investigational drugs and vaccines. This crisis is so acute, WHO declared, that it is ethical to offer interventions with potential benefits but unknown efficacy and side-effects, though every effort should be made to evaluate benefits and risks and share all data generated.

The need for drugs and vaccines was urgent then. With cases now rising exponentially and health systems overwhelmed, it is even greater today. Vaccine safety trials are underway in the USA and the UK, and poised to roll out to Africa soon. But treatments for those with infection are required too. Besides playing a direct part in containing the epidemic, interventions that could improve outcomes for the sick would help to rebuild the confidence of affected communities in health services, a critical step if Ebola is to be overcome.

A fast-track initiative for evaluating investigational drugs was launched in September, 2014.[1] But although the question of whether unproven treatments should be offered at all is now settled, the question of how they should be deployed and tested is not. Still at issue is whether such treatments should be made available only in the context of randomised controlled trials (RCTs) in which patients receive either a new intervention and conventional care, or conventional care alone or with a placebo.

Advocates of this RCT approach[2] state that as this experimental design will create the most robust evidence for the future, and is what regulators are used to, it is the only approach that should be considered. We disagree.

While we concur that RCTs provide robust evidence, and support their use where this is ethical and practical, we do not believe that either consideration is likely to be satisfied in the context of this epidemic. The priority must be to generate data about effectiveness and safety as swiftly as possible, so that the most useful new treatments can be identified for rapid deployment. Alternative trial designs have the potential to do this more quickly, and with greatest social and ethical acceptability.

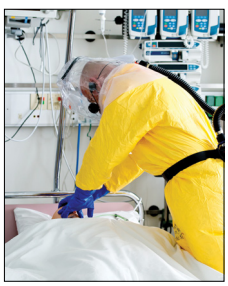
The first objection to RCTs in which investigational drugs plus conventional care are compared purely with conventional care is ethical. Such randomisation is ethical when there is equipoise—when there is genuine uncertainty about whether an untested treatment has benefits or risks that exceed those of conventional care. Equipoise is a useful principle, but it can break down when conventional care offers little benefit and mortality is extremely high. This is precisely the problem with Ebola: current conventional care does not much affect clinical outcomes and mortality is as high as 70%. When conventional care means such a high probability of death, it is problematic to insist on randomising patients to it when the intervention arm holds out at least the possibility of benefit. Ethical arguments are not the same for all levels of risk.

No-one insisted that western medical workers offered zMapp and other investigational products were randomised to receive the drug or conventional care plus a placebo. None of us would consent to be randomised in such circumstances. In cancers with a poor prognosis for which there are no good treatments, evidence from studies without a control group can be accepted as sufficient for deployment, and even for licensing by regulators, with fuller analysis following later. There is no need for rules to be bent or corners to be cut: the necessary procedures already exist, and are used.

The second objection is practical. Even if randomisation were ethically acceptable, it might not be deliverable in the context of health-care systems, and indeed wider social order, that are breaking down as in Liberia, Guinea, and Sierra Leone. Populations who are terrified by the progress of the epidemic, and who lack trust in health-care and aid workers, and in public authorities in the aftermath of civil wars, cannot be expected to offer informed consent to such randomised trials. It is also unclear that any capacity exists to impose controlled conditions during a raging epidemic. Insisting on RCTs could even worsen the epidemic, by undermining trust in the Ebola treatment centres that are central to containing it.

Randomisation is not, moreover, the only way to gather reliable information about the safety and effectiveness of potential Ebola therapies. Indeed, other methods might be more appropriate for achieving the key objective, which is to identify drug regimens that improve outcomes over existing methods of care, quickly, so that WHO can recommend their use and lives can be saved.

One viable approach would be to try different treatments in parallel and at different sites, following observational studies that document mortality under standard care. This approach could effectively triage treatments into those with great benefits that should be rolled out immediately, those with no effect that should be discarded quickly, and those with promise needing follow-up in randomised trials. These trials can be designed adaptively, meaning that patient enrolment can be altered as efficacy data emerge, minimising the numbers of individuals who get ineffective treatments and increasing the numbers getting those that show benefits. This is not different from phase 2 studies as currently conducted and accepted by regulatory authorities for other



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diseases. It will also enable quick follow-up trials of combinations of antivirals and new treatments that have already shown evidence of activity. A different type of RCT might also become an option once more than one drug has shown efficacy—even efficacy in animal models. Then, patients could ethically be randomised to one investigational drug or another. No-one would get only standard care.

We accept that RCTs can generate strong evidence in ordinary circumstances; not, however, in the midst of the worst Ebola epidemic in history. The urgent need is to establish whether new investigational drugs offer survival benefits, and thus which, if any, should be recommended by WHO to save lives. We have innovative but proven trial designs for doing exactly that. We should be using them, rather than doggedly insisting on gold standards that were developed for different settings and purposes.

We declare no competing interests.

*Clement Adebamowo, Oumou Bah-Sow, Fred Binka, Roberto Bruzzone, Arthur Caplan, Jean-François Delfraissy, David Heymann, Peter Horby, Pontiano Kaleebu, Jean-Jacques Muyembe Tamfum, *Piero Olliaro, Peter Piot, Abdul Tejan-Cole, Oyewale Tomori, Aissatou Toure, Els Torreele, John Whitehead*

piero.olliaro@ndm.ox.ac.uk

National Health Research Ethics Committee, Abuja, Nigeria (CA); Hôpital National Ignace Deen, Conakry, Guinea (OB-S); University of Health and Allied Sciences, Ho, Ghana (FB); Hong Kong University-Pasteur Research Pole, School of Public Health, University of Hong Kong, Hong Kong, China (RB); New York University Langone Medical Center, New York, NY, USA (AC); Institut de Microbiologie et Maladies Infectieuses and INSERM, Paris, France (J-FD); Centre on Global Health Security, Chatham House, London, UK (DH); University of Oxford, Oxford, UK (PH); Medical Research Council, Uganda Virus Research Institute, Entebbe, Uganda (PK); Institut National de Recherche Biomedicale, Kinshasa, DR Congo (J-JMT); WHO, Geneva, Switzerland, and University of Oxford, Oxford, UK (PO); London School of Hygiene & Tropical Medicine, London, UK (PP); Open Society Initiative for West Africa, Dakar, Senegal (AT-C); Nigerian Academy of Science, Lagos, Nigeria (OT); Institut Pasteur Dakar, Dakar, Senegal (AT); Open Society Foundations, New York, NY, USA (ET); and Lancaster University, Lancaster, UK (JW)

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Ebola crisis: beliefs and behaviours warrant urgent attention

Why is this 25th outbreak of Ebola in Africa presenting an impending geopolitical crisis?[1]

This is the first recognised outbreak in the west Africa region; the communities are not familiar with Ebola virus. Health beliefs, cultural practices, and human behaviour have combined to fan the dispersal of the disease. The concerns of the west African people, the myths, and conspiracies need to be heard and understood before communities will sufficiently engage to reduce further spread.

Civil unrest is a feature of this humanitarian disaster; suspicion and aggression towards health workers is widespread.[2] The US and British military are indeed best resourced to build field hospitals; but their arrival is being seen on the ground, by some, as an invasion. These fears need to be addressed.

The socioeconomic collapse of the worst affected countries, already causing food insecurity,[3] could exacerbate the destructive effects of Ebola, and create violence. The delivery of effective infection control measures and health care will be challenging under the threat of regional conflict.[4]

This humanitarian disaster will deepen in spite of committed efforts of governments, unless we can understand and address the human beliefs and behaviours fuelling this crisis.

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*Claire Bayntun, Catherine Houlihan, John Edmunds

clairebayntun@doctors.org.uk

London School of Hygiene & Tropical Medicine, London WC1E 7HT, UK

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4 International Crisis Group. Statement on Ebola and Conflict in West Africa. http://www.crisisgroup.org/en/publication-type/media-releases/2014/africa/statement-on-ebola-and-conflict-in-west-africa.aspx (accessed Sept 26, 2014).

Antibiotic sutures against surgical site infections

Markus Diener and colleagues (July 12, p 142)[1] might believe that the study protocol and sample size account for the conflicting findings in the PROUD trial[1] (not showing a prophylactic effect of triclosan-coated sutures against surgical site infection [SSI]) and for findings from smaller randomised controlled trials[2–4] that show benefits for use in antibiotic sutures in prevention of SSI. However, the discrepancy might be more because of differences in baseline characteristics of participants.

Antimicrobial effects of triclosan-coated sutures seem to depend on the length of skin incision, extent of wound contamination at operation, and concurrent diseases amenable to infections, such as diabetes. In a single-centre randomised trial,[2] investigators reported triclosan-coated sutures to be of slight benefit because they decreased the rate of SSIs after open colorectal surgery, but did not change infection