

New ethical considerations in vaccine trials

Malcolm Molyneux

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COMMENTARY

Q1 New ethical considerations in vaccine trials

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5 **ABSTRACT**

Q2 Known and novel pathogens continue to afflict the world's population, and we deploy existing and new vaccines – the best type of weapon we've got – against them. One consequence is that we are accumulating steadily more experience of both the scientific and the ethical requirements of conducting vaccine trials in people. Good science is itself an ethical requirement, as it is meaningless to apply ethical principles to a scientifically flawed product or plan. Bad science can only be bad ethics. And we have learned that ethical principles are a necessity when we apply the benefits of science to the improving of human health.

Q3 Recent epidemics have provided opportunities to expand our understanding of this field and of the many components of it that we recognize to be necessary to the ethical assessment of vaccines.

KEYWORDS: Ethics, vaccine trials, low-income countries, community participation

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Community involvement

10 We have moved a long way from trials in which an unsuspecting population meekly submitted to experimentation by a learned, if well-meaning, body of outsiders whom none of them had ever met or would ever meet again.^{1,2} We now know that the population to be studied is central to both the science and the ethics of a trial. The recent horrifying epidemic of Ebola virus disease (EVD) in West Africa has provided new examples of the necessity and effectiveness of community involvement in a vaccine trial.

15 The people of Sierra Leone recently emerged from a 10-year civil war, following a sequence of slavery, colonial rule and then an oppressive regime. All this may have accounted for their reluctance to trust outsiders. A group wishing to run a trial of a new Ebola candidate vaccine recognized, as investigators now do, the need to engage first with the population on the ground and to understand its concerns.³ They formed a community liaison team, a participant advisory group and a social science team, all consisting mostly of local community members or staff. These teams met and discussed regularly. They discovered that many 'small community leaders' felt that their authority was being undermined by decisions of the 'big' leaders and teams, and that the process for selection of individuals to participate in the trial was perceived to be unfair. The insurance taken out for participants was seen by some as evidence that deaths were to be expected. By understanding these and other issues, the investigators and teams were able to talk through apprehensions. A public lottery system was invented for selection of enrollees. The major joint achievement of this process was to engender an atmosphere of trust that enabled the study to proceed and the community to feel properly involved.³

20 In a multi-country trial of a Group A meningococcal conjugate vaccine,⁴ investigators found it useful to include local

journalists in the liaison team on the ground. They also learned the importance of including husbands and male household heads in preliminary discussions about the trial. They found it useful to bring participants to the laboratory to observe how blood was separated and tested, to allay rumors that blood was being sold overseas. **45**

An aspect of 'community involvement' that is sometimes neglected is consultation with the wider local community, in particular those working in the health care system (to whom individuals enrolled or encountered in the vaccine trial may be referred for routine management of illness), and those in academic or NGO circles who may already be working in the area chosen for the trial.⁵ What research has already been done, or is planned, in the study area? Local clinical or academic experience may be invaluable to the new investigators, and anyway it would be discourteous not to discuss the plans fully with them or even involve them in the study. High levels of government must equally be aware and approving of plans. These communications, like those of local community involvement, are implied by the ethical principle of Respect for Persons and Communities. **50**
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Consent

'Informed consent' requires both effective information and uncoerced agreement to participate. New insights into the consent process have been afforded by recent trials. Describing their experiences in 4 West African sites of a 9-site study of a meningococcal A vaccine, Idoko and others noted and tackled several difficulties:⁴ it was not always easy to identify the local guardian, especially for older children; some local languages were spoken but not written, so that paper information sheets and **65**
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consent forms were problematic; some were suspicious of signing – “Is my word not good enough?”

Several groups have found that pictures, diagrams or objects (syringe, small sample container, filter paper) can help with conveying information during the pre-consent process. To explain biologic concepts, analogies may be useful – e.g. likening antibodies to soldiers.⁶ An individual who has been enrolled in a previous study can provide reassuring information to those considering whether to sign up for a new study. In a study of a trial, one-to-one discussion between a team member and a participant proved to have the greatest success in improving the understanding of informed consent.⁷ It can be valuable to review informed consent at every follow-up visit during the trial.⁶

Whatever methods are used, it is increasingly recognized that *trust* between investigators and the community is a crucial requirement for true consent.³ In a review of HIV vaccine trials in South Africa, the authors write: “mistrust” is as important a barrier to involvement in trials as “misinformation”.⁶

Consent has many site-specific components and sensitivities: there are differences not only between but within countries. The plans for giving information and obtaining consent must be undertaken afresh for any site where a vaccine trial is planned.

95 Ancillary care

Engagement with the community does not end when the trial begins, but should continue during and after it. For many years there have been extensive discussions about the obligations that a research group has – or does not have – to provide trial participants with health benefits that are not related to the trial. CIOMS Guideline 21 makes the slightly odd statement that “sponsors are...not obliged to provide health care services beyond what is necessary for the conduct of research, but it is morally praiseworthy to do so.”⁸ The Helsinki Declaration, even in its latest (seventh) revision⁹ makes no mention of this issue. Common sense suggests that if a trial subject suffers an emergency when in the vicinity of a trial team, everything possible should be done to help. Some trials provide non-emergency services such as treatment of HIV infection or hypertension, measures that can save enrollees a lot of time and trouble and can contribute to trust and cordiality within the study. But if health care provision outside of the trial itself is attempted on too ambitious a scale it can have adverse consequences: it may disrupt local healthcare services, that properly belong to local government; it can generate an undue inducement to individuals to enrol in the trial; it may commence a clinical relationship that cannot eventually be sustained; and it can divert funds or staff time from the task of completing the trial competently.^{10,11} In impoverished areas most studies now at least offer emergency care and provide transport to an appropriate local health facility. Some studies make a point of checking that a referred person has been received and properly cared for.⁶

There is no single blueprint for the provision of ancillary care, except that those planning a trial must give the subject careful thought in advance, discuss it extensively with the local Research Ethics Committee (REC) and with the community,

and incorporate specific plans in the trial protocol that is then reviewed by the REC.

Capacity building

All vaccine trials, especially those conducted in an impoverished area, are opportunities to enhance local capacity. Taking part in the conduct of a trial, especially being involved at planning, review and writing stages, is itself valuable experience for scientists and other staff on the ground. Several large trials have incorporated formal training sessions or enabled local staff to study for higher degrees. In the RTS,S malaria vaccine Phase III multi-site and multi-country study,¹² each study site was linked to a health facility, which was upgraded to permit accurate identification of endpoints and adverse events, the improvements all being available to the population as a whole for routine healthcare provision. Improvements to facilities on the ground are now a common component of vaccine and other trials in areas with limited resources.

Trial design

The Ebola epidemic provided new insights into study design, where science and ethics may sometimes appear to conflict. Dealing with so contagious and deadly a disease, WHO made the unprecedented recommendation for the immediate deployment of a novel vaccine on the sole basis of its safety and immunogenicity in the small number of subjects in a Phase 1 study, and some animal tests. The aim was to give staff and community the chance of early protection – sooner than the many years normally needed for the full trialing and licensing of a vaccine. There was an immediate ethical difficulty: if speed was the purpose, how could it be ethical to run a standard randomized controlled trial (RCT) in which a control group, equally at risk of the disease, would receive some irrelevant alternative vaccine? Yet an RCT is undoubtedly the best tool for assessing a vaccine.

One solution was to use a ring vaccination design,¹³ similar to that which was successfully used in the later stages of the eradication of smallpox. Close contacts of each index patient with Ebola virus disease, and contacts of those contacts, were enrolled and randomized to receive immediate or delayed vaccine, the delay being 3 weeks – the incubation period of 95% of EBV cases. The Ebola epidemic was waning by this time, but the method could be revisited, probably in conjunction with traditional RCTs, should another outbreak occur.

After the trial

Developments in continued community engagement after the trial is over have lagged behind those for the pre-trial period. Our increasing awareness of the community’s point of view and its centrality for the trial have led to progress in this aspect of trials. It is well recognized that participants and their community deserve and appreciate feedback about the results of a trial.¹⁴

More problematic is the question of whether a vaccine that has shown efficacy in a trial should then be given to others in the community. In the case of a multicentre trial of a

meningococcal type A conjugate vaccine,¹⁵ in which the new vaccine performed better than the existing product, WHO recommended that the new vaccine should be given immediately at the end of the trial to those participants in the trial who had not received it (and not to others in the community, who will wait until the new vaccine has been licensed and enough is available for appropriate deployment).

Do investigators adhere to protocols and ethical guidelines?

Trials usually include a Monitor who visits the trial site and assesses to what extent the protocol is adhered to and guidelines are followed. Few of these assessments lead to publications. In a study of several HIV vaccine trials in progress in South Africa, Slack¹⁶ found a high degree of adherence to protocols and to ethical guidelines, and observed that in some respects the researchers' 'practices exceeded current recommendations', particularly in the area of providing prompt and assisted access to local healthcare services for enrollees needing them. In part this commendable difference was due to the fact that guidelines provided little advice about referral to health facilities. More studies of what actually happens on the ground in a variety of vaccine trials would be beneficial to the continued improvement of this discipline. Guidelines are not rules, and in the quoted study the important observation was made that 'protocol declarations are viewed as potentially locking investigators into ethically approved strategies that might prevent flexible, innovative responses'.

The 4 ethical principles applied to vaccine trials

Respect (Autonomy), Beneficence, Non-Maleficence and Justice are all woven into the conduct of vaccine trials. Respect is evident in communication with individuals and communities – including those of local health services and academia – before, during and after a trial, and in being aware of traditions, sensitivities and concerns. Beneficence implies that an efficacious product will benefit trial participants, and that local health and academic capacities will be strengthened. Non-maleficence is written into the protocol's extensive schemes for detecting reactions and adverse events, and must also pay attention to the local health, academic and political context. Justice must ensure that the hardships and benefits of research are distributed with fairness.

Vaccine trials in people share ethical requirements with all forms of human scientific experimentation, but vaccines are special in many ways. They target conditions that cause or have caused enormous devastation to life and health, they harness the body's own mechanisms for defeating pathogens, their delivery is among the simplest and briefest known to health care, and their effect may be prolonged or lifelong. By contrast, the measures required to provide alternative means of prevention or to take care of victims of the same pathogens can be complex, continuing, cumbersome and costly.

Of the 4 primary pillars of health ethics, one is therefore particularly crucial for the study of vaccines: Beneficence. Vaccines can be of such great benefit that failing to put money and effort

into developing and testing them is unethical. This does not mean that the other 3 principles do not apply. They do; and the application of the last 3 principles is all the more important because of the need urged on us by the first – to get on with making and testing vaccines.

Disclosure of potential conflicts of interest

No potential conflicts of interest were disclosed.

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