Chapter 6
Ebola Vaccine Trials

Godfrey B. Tangwa, Katharine Browne and Doris Schroeder

Abstract The Ebola epidemic that broke out in West Africa towards the end of 2013 had been brought under reasonable control by 2015. The epidemic had severely affected three countries. This case study is about a phase I/II clinical trial (testing for safety and immunogenicity) of a candidate Ebola virus vaccine in 2015 in a sub-Saharan African country which had not registered any cases of the Ebola virus disease. The study was designed as a randomized double-blinded trial. It was sponsored and funded by one of the biggest Northern multinational pharmaceutical companies. The protocol received ethics clearance from the relevant national ethics committee. The study was coordinated and managed at the local branch of a big Northern diagnostic laboratory and a laboratory of a local regional hospital. The overall study was a multi-country, multi-site trial aimed at recruiting a total of 3,000 research participants across four or five sub-Saharan African countries. For this country, the recruitment sites were two big cities, each aiming to recruit 200 participants: adults at the first site and children at the second. The target sample size was almost achieved at the first site but, before the study commenced at the second site, some members of (the public) raised the alarm that the government was carelessly risking the health, safety and lives of citizens in the cause of an unproven vaccine that could precipitate a public health disaster. The trial was immediately suspended. A commentary on this case, and on the importance of trust, is provided by Katharine Browne and Doris Schroeder at the end of this chapter. It highlights differences between this case and a phase I Ebola vaccine trial in Canada in 2014.

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Area of Risk of Exploitation

Phase I clinical trials are trials in which the safety of a new treatment is tested in a small group of individuals (often healthy volunteers) to evaluate safety and side effects and to determine dosage. The chances of therapeutic outcomes for the research participants are almost always zero. In this context, the risk of exploitation of low- and middle-income country (LMIC) participants is particularly high, as, due to low education levels, they are more likely to assume that they will benefit personally. For this reason, phase I clinical studies have previously been carried out only in high-income countries. However, they are now increasingly also carried out in LMICs, especially in accordance with community engagement procedures and where the expected outcomes of the study mostly or exclusively benefit LMICs. The same applies, with limitations, to phase II clinical trials, whose main purpose is to assess efficacy. In phase I/II clinical trials in LMICs, it is therefore particularly important to protect research participants.

Specific Case

This case study is about a phase I/II clinical trial (testing for safety and immunogenicity) of a candidate Ebola virus vaccine in a sub-Saharan African country in 2015.

In early 2015, a team of experts from the country's Ministry of Public Health evaluated the availability of facilities for Ebola vaccine trials in certain medical centres and laboratories. The team included members of the country's National Ethics Committee (NEC). Equipment inventoried during this visit, in at least one of the centres, was marked as a previous donation from the owner of the candidate vaccine. After these visits, two urban medical centres were retained for the Ebola vaccine study.

The visits occurred after the Ebola epidemic that had broken out in West Africa towards the end of 2013 and that had been brought under reasonable control by 2015. The epidemic had severely affected three countries. However, the country of the candidate vaccine trial had not registered any cases of the Ebola virus disease.

The study was designed as a randomized double-blinded trial in which half of the research participants would receive the candidate vaccine and the other half a placebo. The study was sponsored and funded by one of the biggest Northern multinational pharmaceutical companies, globally well known and highly respected. The first medical centre was to recruit 200 adult research participants and the second 200 children. The protocol of the study, at least for the first recruitment site,

received ethics approbation from the NEC. Recruitment was nearing completion at the first site when, following complaints from some members of the public, the study was suspended.

The suspension order was apparently made by word of mouth. The Minister of Public Health who had initially announced the commencement of the study over the radio did not announce its suspension through any public media. However, he did write to the principal investigator (PI) at the local branch of the Northern diagnostic laboratory to explain that the study had been suspended due to public protests and that the trial involving children would now be withdrawn too. The general public, as well as the research participants and their families and communities, knew little about the study, let alone why it had been suspended, and therefore permitted themselves the most fanciful speculation about it.[1]

Case Analysis

This case bristles with ethical problems and issues that go beyond any simple identification of instances of North-South "ethics dumping". It involves subterfuges to circumvent standard regulatory procedures and discretion bordering on secrecy – approaches that would be inconceivable in high-income countries, or anywhere else where there is sufficient awareness of the stakes of biomedical research and the ethics of clinical research, particularly that involving human research participants.

The risk of exploitation in this case is not limited to a single rubric such as "no benefit sharing" or "inadequate informed consent process", but relates rather to the exploitation of the general weaknesses and inadequacies of an entire system, particularly its lack of a credible and adequate research governance and regulatory framework. This suggests double standards that would also be inconceivable in a high-income country.

International regulatory texts are simple and clear on the procedural rules for the ethically acceptable conduct of medical research, particularly clinical trials, with human beings as research participants. The *Declaration of Helsinki*, for instance, states:

> The research protocol must be submitted for consideration, comment, guidance and approval to the concerned research ethics committee before the study begins. This committee must *be transparent in its functioning*, must be *independent of the researcher*, the sponsor and any other undue influence and must be *duly qualified* (WMA 2013: art. 23) (emphasis added).

Regarding "post-trial provisions", the declaration states:

> In advance of a clinical trial, sponsors, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention

[1]For popular concerns raised in such contexts, see Geissler and Pool (2006).

> identified as beneficial in the trial. This information must also be disclosed to participants during the informed consent process (WMA 2013: art. 34).

These minimal conditions were evidently not fulfilled for this trial. The members of the ethics committee that approved the study were all appointees by decree of the Minister of Public Health and functioned within a civil service system where obedience to hierarchical superiors was regarded as a duty. It is the view of this author that by assuming sponsorship of the clinical trial in this case, the Minister virtually made it the duty of all within the Ministry of Public Health to help facilitate its accomplishment. This would explain why some members of the ethics committee were involved in prior site preparations for the trial, which was inappropriate for an ethics committee as it compromised ethical oversight of the study and put the independence and transparency of the ethics committee in serious doubt.

There is no doubt that all the members of the approving ethics committee (which in fact acts as the national ethics committee) are highly qualified in their fields, but this does not automatically make them experts in ethics review. The expertise represented in the committee is roughly as follows: a haematologist, a parasitologist/epidemiologist, a pneumological epidemiologist, a sociologist, a demographer, an x-ray oncologist, a pathologist, a jurist, a parasitologist, a surgeon, a microbiologist/pharmacist, a dental surgeon, an expert in the science of education, a paediatrician, a civil society member, a traditional practitioner, an expert on Islamic religion and two community members. This is a highly impressive committee for science review, perhaps, but not necessarily for ethics review, if no research ethics training has been provided. And even if such training has been provided, which usually happens by way of workshops or symposia, every research ethics committee still needs an ethics expert, meaning someone whose main business and concern as a member of the committee is ethics aspects of and ethics issues in the protocol.

The study was suspended before the recruitment of children had begun at the second site. The inclusion of children in a clinical study designed for testing safety and immunogenicity is a big ethical issue for which, at best, no justification was available for this study. All over Africa, women and children, because of their vulnerability, high rate of morbidity, easy availability, naivety and trustfulness, bear a heavy burden of clinical research. A competent ethics committee would have checked the burden of research participation against the benefits for research participants and their immediate communities, especially where children were involved.

The whole study involved structures and procedures that, on the surface, appeared to conform to ethics demands but, in reality, violated the principles of research participant protection that are paramount in research ethics. The following section analyses the case further, with specific reference to the informed consent documentation.

The Informed Consent Process

The potential research participant information for this study contained inadequacies and issues that any qualified ethics committee should have noticed and raised with the investigators for redress or amelioration before subject recruitment commenced.

Regarding the informed consent process, the *Declaration of Helsinki* states:

> [E]ach potential subject must be adequately informed of the aims, methods, sources of funding, any possible conflicts of interest, institutional affiliations of the researcher, the anticipated benefits and potential risks of the study and the discomfort it may entail, post-study provisions and any other relevant aspects of the study (WMA 2013: art. 26) (emphasis added).

An analysis of the information sheets given to the potential participants in this clinical trial shows serious omissions and inappropriate or misleading language for the context (see also below). Participants were not taken through any informed consent process other than being approached individually by the study physicians or their agents at the chosen site of the study, given the information sheets to take home and asked to come back the next day to sign the informed consent form, followed by procedural instructions, and payment to them of a sum of approximately US$20. Furthermore, there was no process of community engagement beyond the media announcement by the Minister of Public Health emphasizing that the study had been approved by the World Health Organization (WHO) and was simultaneously taking place in many countries. In retrospect, the Minister's announcement could be judged an inducement which played down the potential stakes and risks of the study by referring to the approval of the WHO and the fact that other countries had accepted the trial.

Some of the issues and questions addressed in the five-page prospective participants' information sheet are quoted below, in italics. Each excerpt is followed by my attempt to review and critique it in the way a competent and vigilant ethics committee might have done.

> ***Why is this clinical study being done?***
>
> *This study is done to test a vaccine against Ebola to make sure that it is safe and that it brings about a protective response. You can get Ebola by being in direct contact with the blood or other body fluids of a person who is already sick with Ebola. People infected with Ebola can have many different symptoms, like fever, severe headache, muscle pain, weakness, feeling tired, diarrhoea, vomiting, stomach pain and unexplained bleeding or bruising. Ebola disease can be very severe and is a life-threatening disease.*

Only the first sentence of the above response addresses the question asked. But it is misleading and confusing to state that the study is being done "to test a vaccine against Ebola" whereas the answer to a subsequent question below states that "there are no vaccines or treatment against the Ebola virus". The candidate vaccine ought to be called and described accurately for what it is. The rest of the response is not relevant to the question: it answers another question that has not been asked, namely: what is Ebola and how does one get it?

Who can take part in this study?

You can take part in this study if you are at least 18 years old, healthy, not taking part in another study, have not been in a country affected by the Ebola epidemic (Sierra Leone, Liberia and Guinea) and have not been in contact with someone who has Ebola in the last 3 weeks.

In the country of this study, the age of majority and consent is 21. Since clinical studies need to conform to local laws and regulations, the age of participation here should be 21, not 18; or else it should be explained that those below 21 would require the proxy consent of their parent or legal guardian in addition to their own assent.

Considering the issue of fairness in the recruitment of study participants, it may be questionable to make the mere fact of having been to an Ebola country and even of having been in contact with an Ebola patient – without, however, contracting the disease – an exclusion criterion for the study.

Which vaccine will you get?

You will get the Ebola vaccine, either at the start of the study, or after 6 months into the study. At the start of the study, half of the people in the study (about 1,500 people) will get the Ebola vaccine and the rest of the people will get a placebo (dummy vaccine that looks like a real vaccine but does not have active components in it). Neither you nor the study doctor can choose or will know which vaccine you receive. This will be randomly decided by a computer (like the flip of a coin). We will only tell you and the study doctor which vaccine you received after 6 months into the study, or if there is an emergency.

This response repeatedly refers to an "Ebola vaccine", even though it does not yet exist. It also fails to explain in simple ordinary language such terms as "placebo", "dummy vaccine" and "active components", and to illustrate what may count as an "emergency". Informed consent processes must avoid jargon, especially in LMIC settings.

What does this study involve?

The first study visit, called a Screening visit, is to check if you can take part in the study. The study doctor will ask you some questions, do a physical examination and take some blood to test blood factors. If you are a woman who can get pregnant, the study doctor will also ask for a pregnancy test. If the Screening shows that you can take part in the study, you will be in the study for about 1 year. Half of the people to join the study will have extra study procedures done. ... if you are part of the group of people that does NOT need extra procedures you will: visit the vaccination centre 4 times after the Screening on Day 0, month 1, month 3 (phone call/home visits), month 6, month 9 (phone call/home visit) and month 12. At Day 0 visit, you will be vaccinated. This is an injection in the muscle of your upper arm. After vaccination, you need to stay at the vaccination centre for at least 30 minutes for observation. If you receive the dummy vaccine at the first visit, you will be vaccinated with the Ebola vaccine 6 months later. ... During the entire study, we will check if you have any serious medical conditions. You will not have blood taken during the rest of the study.

First, here too the use of technical medical terms is problematic ("screening visit", "blood factors", "extra study procedures", "muscle of your upper arm", "serious medical conditions"). Second, this may make a good entry in the notebook

of the investigator but will not necessarily be meaningful to a prospective subject without prior verbal explanation. What, for instance, is a barely literate person to make of "Day 0, month 1, month 3 (phone call/home visits)"? Would s/he not be wondering how a day could be zero and if s/he would be required to telephone someone or visit them at home?

What about pregnancy?

We do not know yet if the Ebola vaccine may have an effect on an unborn baby. That is why you should not take part in this study if you are pregnant or trying to get pregnant. … You will need to use birth control during the first 7 months you take part in this study. Tell the study doctor if you are pregnant during the first 7 months of the study. The doctor will follow you up until the delivery of the baby.

This explanation about pregnancy is not free of ambiguity. It is quite clear that I should not take part in the study if I am pregnant or want to get pregnant. It is also clear that, if I want to have sex during the seven months of the study, I should use contraception. But telling me that I should inform the study doctor if I get pregnant during the first seven months of the study so that s/he can follow me up until the delivery of my baby is rather confusing. A study participant might say: "Getting pregnant and being followed up until delivery is what I want most. So why does the informed consent documentation say that I should not take part in the study if I am pregnant or want to get pregnant?" This paragraph crucially fails to explain that contraception can sometimes fail because no method of contraception or birth control is 100% effective except abstinence.

What benefits can you expect?

You may not benefit from the Ebola vaccine because we do not know yet if the vaccine will be able to protect people against Ebola virus.

This is at best an incomplete response to the question. Of course you do not know yet if the vaccine will be able to protect people against the Ebola virus; that is the whole purpose of the trial test. But what happens if/when it does prove to be able to protect people against the Ebola virus disease? How is article 34 on "Post-Trial Provisions" of the *Declaration of Helsinki* going to be respected?

What side effects or risks can you expect?

There is a very small risk that you could have an allergic reaction after vaccination. … That is why it is important that you stay at the vaccination centre for at least 30 minutes after vaccination, where all medical tools are available to treat an allergic reaction.

To avoid misunderstanding among research participants with low literacy and education levels, it would be better to rephrase this response in terms of the possibility, not how small the risk – "It is possible that you could have an allergic reaction" – followed by an explanation of what an allergic reaction is.

Are there other vaccines or treatments?

So far, there are no vaccines or treatment against the Ebola virus.

For clarity, the question should be "Are there other vaccines or treatments against Ebola?" Also note the confusion if one compares this statement with earlier mentions of a vaccine, for instance in "You will get the Ebola vaccine …" (see above).

What happens if you leave the study?

If you leave the study we will keep and use the information and samples we collected before you left the study. We will ask you to return to the vaccination centre one more time for a safety follow-up.

The obvious follow-up questions not addressed here are: Why would you keep and use the information and samples you collected even when I have decided to leave the study? And why should I return to the vaccination centre again after I have decided to leave? What safety follow-up are you talking about?

Who will be looking at the information from this study?

Your information will be protected in accordance with the most stringent applicable law.

When you sign/thumb print this consent form you agree that your information can be viewed and used by site staff, [the pharmaceutical company], agencies and independent ethics committee. ... [the pharmaceutical company] may publish the results but your name will not appear in any publication. If you withdraw consent to use your personal information you will no longer be able to continue in the study.

The questions that need addressing here are: what is "the most stringent applicable law" that will protect my information, and why should my name not appear in any publication of the results in spite of my contribution to it? (See also the supplementary report after this case study, which describes the pride with which Canadian research participants in a phase I Ebola vaccine trial made their names public.)

What happens if you get injured while taking part in this study?

If you are harmed by the vaccination in the study or by any of the study procedures, you will be compensated. Your study doctor can give you information about how to obtain compensation in case of injury. You will not be paid for taking part in this study but you will be paid reasonable travel fees to attend to study visits at the vaccination centre.

This question needs a fuller and clearer answer. Compensation for study-related injury should not vaguely be referred to the study doctor; it should be explained clearly. "You will not be paid… but you will be paid…" is not a good formulation in informed consent information and needs to be rephrased less ambiguously or even misleadingly.

The informed consent form (certificate) states:

The study has been explained to me. I have read the information or have had the information read to me. I have been given enough time to make a decision. I have had the chance to ask questions and I am happy with the answers that I have been given. I have been told that I can change my mind at any time and stop taking part in the study without giving any reason. By signing/thumb printing this form I agree:

1. To take part in the study
2. That my information is used as described in this form
3. That my blood samples are used as described in this form

Tick as appropriate (this decision will not affect your ability to take part in the study):

YES. My samples may also be used for future research (at the time of the study or after the study is finished) not described in this form with prior approval of the Ethics Committee
NO. Do not use my samples for future research (at the time of the study or after the study is finished) not described in this form.

The tickable options above are about something as important as the use of samples for unknown future research. This ought to be discussed and justified in information designed for the prospective participant. As formulated here, the section in parentheses is not clear and is liable to be quite confusing: "at the time of the study or after the study is finished" should perhaps be changed simply to "after this study is finished".

Talking to two of the potential research participants suggested that the main motivations for participation were the incentives – the health care benefits and the money paid. Of course, there are limits to the conclusions one can draw from talking to only two people, but the literature shows that financial incentives and access to health care are a major driver for enrolment in studies in LMICs (Mfutso-Bengo et al. 2008; Mduluza et al. 2013). For this reason the case raises concerns about undue inducements.

Conclusion

The regulation of human subject research and particularly of clinical research is quite advanced around the globe, to the extent that we can talk about a regulatory infrastructure, whose presence or absence in any given context should indicate a priori whether or not research involving human subjects can ethically be conducted within that context. Such regulatory infrastructure would include, in a non-authoritarian and genuinely democratic context, a legal framework that respects fundamental human rights, especially freedom of inquiry and expression, overseen by well-constituted, qualified and genuinely independent ethics review committees.

The absence of such infrastructure or doubt about its genuineness, in spite of appearances, delimits a no-go area for ethical research. The verifiable existence of such an infrastructure should be a precondition for human subject research, especially in resource-destitute settings and particularly in the first two phases of investigation. Transparency must be part and parcel of any procedures where publicly available regulations need to be followed. Systemic faults tend to render compliance with good procedural rules and practices not only difficult, but impossible. It is not just difficult, but impossible, to carry water in a straw basket for any distance.

Supplement to the Ebola Vaccine Trial Case – The Importance of Trust

This is an excerpt from a Canadian newspaper article:

> Hundreds of Nova Scotians are volunteering to be injected with an experimental vaccine that might cause aches and fever – but could protect against the Ebola virus.
>
> Within minutes of the Nov. 14 announcement that Halifax's IWK Health Centre was chosen to hold the clinical trial to test Canada's Ebola vaccine, the phones started ringing and e-mails began arriving from people who wanted to participate. A week later, the trial team has heard from about 300 people – it only needs 40 healthy individuals, between 18 and 65, for this first-phase trial (Taber 2014).

The phase I trial for the Canadian-developed Ebola vaccine (VSVΔG-ZEBOV) was conducted at the Izaak Walton Killam Health Centre in Halifax, Nova Scotia. The trial involved 11 clinic visits over six months, each requiring a blood draw. Participants received CAD 1,125 for their participation in the entire trial.

One of the authors of this supplement, Katharine Browne, is involved in a study examining the factors that motivate healthy volunteers to participate in phase I vaccine trials. The study involves a survey of the motivations of healthy volunteers for the Canadian phase I Ebola vaccine trial, as well as a phase I trial for a PAL adjuvant.[2] The central hypotheses of the study are that:

1. The financial incentive will be the dominant motivation that participants identify.
2. Other motivations will include a desire to contribute to the development of a vaccine, and a desire to help others.
3. The high-profile nature of the Ebola vaccine trial will play a factor in participant motivations.

Surprisingly, and contrary to the first hypothesis, preliminary findings from the study reveal that financial incentives are neither the sole nor the main determinants in motivating individuals to participate in vaccine trials. The findings do, however, confirm the second hypothesis: that participant motivations include desires to help develop a new vaccine and to help others. One research participant explained to the media that participating in the trial had been a life-changing experience for her (CTVNews.ca Staff 2014). When asked about the financial incentive provided for participation, she said that she would put it towards her university studies. She also noted that another research participant had donated the money he received for participating to a children's charity (CTVNews.ca Staff 2014). Concerning the third hypothesis, the findings are unable to confirm or deny that the high-profile nature of the Ebola vaccine trial contributed to trial participation.

[2]An adjuvant is an immune booster that can be added to a vaccine. PAL is the name of a particular adjuvant.

The study findings, along with the anecdotes from trial participants, support a general trend away from the selfish actor model that underlies classical economic theory and that informs policies and practice, including payment for research participants.

The Canadian experience of the phase I Ebola vaccine trial provides a remarkable contrast to the almost identical study at the African site. One possible explanation for the over-recruitment at the Canadian site compared with the public outcry at the African site could be the extent to which the two trials differ in the levels of trust between research participants and researchers. The suggestion here is that there is a lack of trust in North-South collaborations and that this dramatically affects the recruitment of research participants. Further research is required to confirm or deny this hypothesis. To enhance trust in such collaborations, we re-emphasize Tangwa's two main conjectures:

1. The verifiable existence of an infrastructure that respects fundamental human rights should be a precondition for medical research involving human participants, especially in LMICs and particularly in the first two phases of investigation.
2. Transparency is essential when conducting trials in LMICs.

In addition, Tangwa's analysis of the informed consent documentation reveals a notable ignorance of local requirements (e.g. researchers seeming unaware of the local age of consent). This is likely to contribute to distrust in North-South collaborations.

One could venture that the non-existence of a reliable governance structure and non-transparency, combined with insensitivity to local requirements, have a major impact on trust.

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