Emergency Ebola Anthropology Network
Advisory Brief: Culture and Clinical Trials

This advisory brief aims to provide anthropologically informed guidance to governmental and humanitarian actors involved in the Ebola response at local, national and international levels, about clinical trials for Ebola treatments, therapies and vaccines. It serves to (1) clarify and demystify some of the scientific and technical discussions around the numerous clinical trials; (2) revisit issues surrounding the compassionate use of experimental medications and therapies in and after an emergency; and (3) provide a summary of the cultural, institutional and historical factors that impact the organization of clinical trials in the three-most affected countries, Sierra Leone, Liberia and Guinea.

This brief does not consider the clinical-scientific merits or deficits of the vaccine trials, the class history of candidates, or choices in the development of specific therapeutics and vaccines. This is beyond the scope of the Network's collective expertise.[1] Rather, we aim to provide contextual information and a broad social-moral framework of operational use to the response and its multiple stakeholders. Whilst policy recommendations are made, we restrict much of our analyses to issues identified, observed or reported through engagement with local, national and international partners and multilateral agencies.

Key considerations

- The international collaborative consortia which have emerged to accelerate pharmaceutical development in the Ebola response is unprecedented.
- The United States, France, and the United Kingdom have conducted clinical trials and experimental medicine in Guinea, Liberia, and Sierra Leone for over a century (for example, in relation to polio, leprosy, hepatitis). These experiments are known to have continued throughout the region until the 1990s. Local populations have knowledge and experiences of this experimentation and may have good reason to be distrustful of medical trials to control Ebola Virus Disease (EVD).
- Local populations may not be aware that many of the drugs and vaccines to be tested are first generation and not final approved products. Despite the fact that most drugs and vaccines fail in development, EVD research is being fast-tracked in human populations because of the severity of the epidemic. A percentage of the tested drugs and vaccines are likely to fail. Local populations must be informed and understand this.
- Local populations may not be aware that risks presented during the informed consent process are based on non-comparable testing conditions, and that local conditions may result in different (potentially worse) outcomes. Local populations may not be aware that specific risks (age, sex, nutritional status, disease severity, comorbidities) may impact therapeutic efficacy. They may also be unaware that due to study limitations, many adverse events and associated risks could remain unknown even after the completion of randomized clinical trials (RCTs).
- A failure to assure cultural appropriateness and to make information accessible, relevant and understandable is tantamount to a failure to protect human subjects. If this occurs on a large scale, it may result in human rights violations.
- Communities may have valid justification for conflict with current clinical trials for EVD.
- No agreements should be made that will provide immunity from prosecution for human rights violations to international, bilateral, or private research organizations engaged in biomedical research for EVD.

[1] This brief summarizes discussions facilitated by the Emergency Ebola Anthropology Network in response to a Request for Information on clinical trials and blood donation. The brief also drew on Anthropology & Ebola Clinical Research Working Group Document produced by the UK Ebola Anthropology Platform.

Structural issues in the administration of clinical trials

- Hundreds of pharmaceutical companies have approached the World Health Organization (WHO) to have their candidate therapeutic products for EVD tested among West African populations. Substantial global economic and political pressures to address the current crisis have inevitably impacted research processes, protocols, and practices. Inequalities in access to information, resources and authority (informational and power asymmetries), affect the ability of national governments to set standards and regulate the administration of clinical trials. Relationships between African states and former colonial powers also impact national governments' ability to regulate scientific authority.
- The WHO declaration of a global health emergency should not be used as a pathway for bypassing national capacities and sovereignties.
- The loosening of restrictions on non-validated agents for emergency use should not result in national statutes and laws being bypassed or manipulated.
- Prescribing drugs is different from testing medications for the purposes of research. Doctors who prescribe medical interventions to a class of patients for the purpose of discovery are engaged in medical research. Doing so without medical justification, a rigorous informed consent process, approval from a national or international Institutional Review Board (IRB) and without adhering to a well designed clinical and research plan, constitutes 'rogue' research.
- Pre-existing structural deficits (including weak governance structures and regulatory environments and limited health systems resources) will likely inhibit governments' abilities to restrain 'rogue' researchers.
- There are socio-political hazards surrounding public perceptions of clinical trials. Reported questions such as 'If the experiment is damaging, why did government or international groups experiment on us?' and 'If the experiment is beneficial, why was it not used earlier and why is it not more widely available?' express valid concerns that need to be addressed with relevant information and in as much detail as possible.

Recommendations

- Legal and ethical review frameworks within Sierra Leone, Liberia and Guinea must be able to accommodate clinical trials and the compassionate use of experimental drugs. Each nation-state should have a WHO recognized national regulatory authority at the central level.
- If Sierra Leone, Liberia and Guinea lack the capacity to self-regulate clinical trials, a rapid capacity-building process at national and regional levels should be facilitated and adequately resourced. This should support nation-states in the use of local governance structures to administer clinical trial activities amongst their populations.
- National, pan-African and international review boards for the protection of human subjects should officially register and sanction the engagement of local populations in medical emergencies in low-income countries and protect them from being exploited by rogue research.
- National and international medical licensing associations should take steps to penalize rogue researchers and medical professionals involved in unethical or deceptive practices.
- A roadmap indicating how clinical trials can be used to support the long-term goal of health system strengthening (HSS) should be developed.
- In-country auditing capacity should be established to track global financial flows around clinical trials.
- We recommend the immediate establishment of a high-level independent investigative and reporting board to study the implementation of clinical trials from advance preparation to trial conclusion in all three countries. This should pay specific attention to issues of sovereignty, scientific authority, national and community-based engagement and capacity building and longitudinal clinical implications. The African Vaccine Regulatory Forum (AVAREF), African Medicines Regulatory Harmonization (AMRH) and the WHO-coordinated networks of regulators may be able to play significant roles in this area. The UK Ebola Anthropology Platform Working Group on Clinical Trials has also proposed to serve in this capacity.

- We recommend the formation of a collaborative initiative funded by the international community to inform African populations about clinical trials at a national level. Communications should undergo an independent peer-review process to ensure that messaging does not introduce marketing or bias into public debates and discussions about clinical trials.

Social consultation and the process for securing informed consent

- Clinical research can involve great risks to individuals, but in the context of collapsed health systems, it also constitutes a burden for local populations. Informed consent must therefore involve both individual agreement and a meaningful process of community consultation, consent, and follow-up.
- The current convention for indicating informed consent is to obtain a signature, thumbprint or verbal consent in response to informed consent scripts. However, the process for securing informed consent must be understood to be relational and more than 'just getting a form signed'.
- Individual informed consent is necessary to assure an individual's voluntary participation in the research process. Community informed consent is necessary to explain the risks to the participant in relation to the social networks that support individual study participants. This is an important component of encouraging community responsibility for the success of a clinical trial by creating informed social engagement to support short- and long-term surveillance and reporting. It enables the communication of emerging conflicts between the community and trial (or observational study), and can help resolve issues in an open, transparent, accountable and structured format.
- Current protocols indicate the need for consultation with local 'leaders' including traditional healers, paramount chiefs, religious specialists, youth groups and local NGOs. This is incomplete shorthand for the concept of 'community' in 'community engagement'. Community engagement extends well beyond interaction with designated community leaders, who represent the first tier of community leadership and are not necessarily key decision makers. It also involves a second tier of crosscutting social constituencies that involve economic, political, religious, gender and age affiliations, and a third, more intimate tier of extended familial and kinship networks. Each affect an individual's ability to indicate informed consent.
- Throughout the region, there is a wide range of attitudes towards control over the body. Some actors, such as husbands, older men and older women may be able to make decisions about their physical body without extensive family consultation. In contrast, the bodies of young people (particularly young women, both married and unmarried) may not be entirely subject to their control and young people may be seen as too inexperienced to make decisions about their bodies alone.
- Young people make substantive contributions to family and kinship networks. Their short-term removal from household economic activities, longer-term debility or death from side effects, may affect a large group of people. Therefore, communal informed consent is necessary to assure that there are not social or economic repercussions for participants, or undue or unintended hardship imposed on households.
- Blood is a highly salient component of local knowledge systems and is seen as a shared resource within kinship networks. For example, a grandfather may oppose his grandson giving away 'his' blood through therapeutic blood transfusion. Concerns about the giving of blood, the spoiling or contamination of blood and the misappropriation of blood can have ongoing social ramifications for donors, particularly in the domain of marriage and reproduction. Women, for example, may be seen to have had their blood 'spoiled' and therefore be unsuitable for marriage and motherhood.
- Clinical trials offer an opportunity for the economic exploitation of participants' biological assets. Participants must be apprised of their economic and ethical rights if their bio-property (e.g. blood serum) is used for commercial purposes. They must also be informed how to protect their proprietary rights.
- Efforts are underway to address people's concerns and fears about clinical trials in proactive and transparent ways. Typically, an informed consent process involves the communication of risks to participants prior to study enrollment. In the context of EVD, a successful informed consent process

may be one in which many individuals and communities choose *not* to participate in clinical trials. It is only through a level of refusal that we can be sure that people have exercised their right to decline participation.

- Health workers have been signaled as a high priority population for participation in RCTs. It should be noted that health professionals will have different levels of knowledge about the risks and benefits of clinical trials.

Recommendations

- We recommend that informed consent be carried out through a meaningful process of local consultation and that alternative, locally valid benchmarks for informed consent be rapidly developed.
- Adequate time must be built into models and procedures for sharing information and securing informed consent at an individual and community level.
- In order to mitigate risk, recent, accurate and comprehensible information about the best evidence for the safety and effectiveness of the interventions must be explained and made understandable to study participants and their families prior to their involvement and at the start of the consent process.
- All clinical research trials should designate an ombudsman to serve as liaison between communities, national governments and the research initiative. This focal person should be empowered to hear, address and resolve community concerns, conflicts or criticisms of the research process or its effects. Contact information and procedures to report violations of ethics or issues of malpractice or poor conduct should be widely distributed to local populations. This information should be included in all informed consent documents. We recommend that national governments, aid partners and international organizations preempt post-hoc examinations of violations by presuming that conflicts, errors, and ethical violations may occur.
- It is crucial that compensation envisioned for individual donors also acknowledges the cost of participation to their households and families. Resources should fairly remunerate the loss of a working member's time and presence. It is also important to frame this compensation as a 'gift' to 'thank' the family for their collective contribution and service, since the symbolic implications of what may be understood as 'selling' body parts and substances (i.e. blood) on the market can be devastating.

The limitations of informed consent

- The practice of informed consent is meant to communicate potential risks to participants in clinical research trials and requires the full disclosure of possible short- and long-term risks to participants. Because of the fast tracking of EVD research, many potential risks remain unknown. Poor healthcare structures and a high level of undocumented and unknown pre-existing health conditions make known risks much more uncertain. This must be communicated to participants.
- Informed consent also requires the full disclosures of short- and long-term benefits to the participant. Many of these benefits currently remain undisclosed, and in some cases, are yet to be determined. The following key questions should be considered:
  - Will participants, families, communities, or countries be entitled to targeted or widespread immunization at no cost when a successful vaccine is approved?
  - Why will some communities be asked to participate, whilst others are not? Will the criteria for individual and community inclusion be made known to citizens?
  - How will participants receive long-term medical care for any short- mid- and/or long-term conditions and disabilities resulting from adverse events following their participation in trials or eventual immunization, especially if such conditions may emerge months or years after their involvement?
  - What criteria will be established and who will be considered in the determination of adverse events associated with experimental products compared to natural causes?

  - If a participant is incapacitated or dies during a trial, will their family be entitled to damages or long-term support for the economic losses caused by the incapacitation or death of their family member?

- Network members have learned that some institutions involved in clinical trials are using marketing approaches to persuade communities to participate. It has been reported that, at the local level, it was suggested that vaccines would be made available to local populations first, or that they would be made widely available. Any non-factual claims constitute a form of deception that limits informed consent. We oppose the use of deceptive or biased communication practices in order to encourage participation or enhance local acceptability of enrollment.
- It has also been brought to the attention of Network members that blood samples drawn for diagnostic purposes are being released to researchers for additional research activities without the informed consent of the human subjects. We have been informed that this is technically legal under current definitions of what constitutes an epidemic, but we maintain that this activity may be ethically suspect, and all such activity must be registered and reviewed by an independent ethical oversight committee.

The use of placebos, experimental drugs and vaccines in human subjects

- All populations should share in the risks *and* rewards of clinical trials.
- Internationally, there is an ongoing and volatile debate over whether or not drug trials should include placebos to statistically determine efficacy, or exclude placebos on humanitarian grounds. The case for randomized clinical trials (using placebos) is preferable for determining the drug's utility. Non-placebo experimental use is advised for scarce drugs in order to gain as much information as possible with limited resources.
- In West Africa, confounding issues may make it difficult to statistically discriminate between treatment and placebo. A strategy to address this analytically must be made clear in study protocols.
- There are real differences in the administration of experimental therapies and drugs in high-, middle- and low-income countries. Patients in the United States and Europe are offered one, two or even three experimental drugs or therapies in Level 4 (highest care) supportive treatment. No placebos have been administered among this population. Patients treated in Africa are likely to receive, at most, one experimental therapy or vaccine. Placebos may be administered. Treatment is likely to be delivered in primitive or transient facilities with a comparatively low level of supportive care. There must be clear strategies to acknowledge and, when possible, address these inequities in study designs.

Recommendations

- Long-term surveillance and response capabilities must be instated to gather data and treat any long-term health consequences for trial participants (and Ebola survivors).
- Studies should design-in the training and sustained salary support for longitudinal pharmaco-vigilance by local health workers.
- Studies should design-in the participation of teams of international medical experts in formal vaccine trials or compassionate-use of vaccines.
- There should be international media coverage showing that the world shares in the risks and the benefits of these vaccine trials.