Global Forum on Bioethics in Research

Meeting report:

Emerging epidemic infections and experimental medical treatments

Annecy, France

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Global Forum on Bioethics in Research

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Executive Summary

Grounding and Justification: The Global Forum on Bioethics in Research convened at the Fondation Mérieux in Annecy, France, in November 2015, to explore the ethical issues related to "Emerging epidemic infections and experimental medical treatments". With experts in bioethics, epidemiology, anthropology, public policy and clinical research from over 35 countries, the meeting used LMIC case study presentations and first hand experiences from the recent Ebola epidemic to ensure complex ethical issues remained grounded in the practical realities of how research is conducted during epidemics.

The inherent challenges of social and economic disruption posed by epidemics are often in the context of poor basic health infrastructures, limited in-country personnel and an often challenging political environment. Particular ethical pressures for research arise in these settings because of (i) high uncontrolled morbidity and/or mortality, (ii) scarcity of resources and (iii) time pressure on decisions, based on incomplete information of uncertain validity. While guidance for undertaking research in emergency settings exists, lessons learned from previous epidemics are rarely remembered.

Trust: Trust in research and researchers in an emergency epidemic situation is often fragile and frequently lacking, but earning trustworthiness is a complex, multi-factorial process. Populations affected by epidemics are often stigmatised, isolated and fearfully perceived as 'other'. Pre-existing distrust of government institutions and foreign intervention may prove a significant barrier to the most ethically conducted research. Ebola vaccine trials in Guinea and Sierra Leone addressed the issue of trust by first vaccinating the coordinator of the national Ebola response and other prominent health leaders. Meeting participants agreed that understanding and addressing the local context for research through continuous communication, transparency and highly accessible systems of accountability are required to engender trust in a research project during an epidemic. Community engagement and anthropological research can inform these efforts.

Community engagement efforts must be especially cognisant of the potential to confuse the offer of health care with experimental interventions that may have less evidence underpinning effectiveness than normal therapeutic treatment trials. Involvement of local expertise is an effective way to understand and counter community tensions as well as build research and ethical capacity locally. Researchers can benefit from working with an organization with long term involvement and a trustworthy reputation in a community. During an epidemic, pre-existing systems for obtaining permission to conduct new research may be disrupted, but a trustworthy ethical review process that includes both local and international research ethics committees can support rapid research efforts. Action is needed to enhance the visibility and credibility of research ethics committees within local communities to guarantee research is conducted ethically. For example, professionalization may bolster the role and reputation of local research ethics committees in making decisions about research proposals.

Consent: The question of whether "free" consent can be given under the "coercive" conditions of an epidemic scenario must be considered. In normal clinical settings it might be considered ethical to offer untried medicines when the alternative is death. However, in the midst of an untreatable infection, it is extremely difficult for participants to avoid therapeutic misconceptions – any experimental treatment may be perceived as a potential miracle cure and the opportunity to enrol in a trial, the only option for care. The ethical concern with this option during an epidemic, however, is that testing an experimental therapeutic agent may be considered highly problematic opportunism. Research does not need to be set up in opposition to clinical care though. For example, standard care could be given, with additional therapeutic use monitored. One resolution

to this perceived tension between research and clinical care would be to only start research once the epidemic is under control. However, most Ebola related trials conducted at this point in the outbreak were inconclusive due to the lack of statistically significant enrolment.

Researchers during epidemic outbreaks also report challenges to the consent process with quarantined participants, proxy consent with incapacitated participants and children when parents are absent. There's continued disagreement on the question of broad consent for future use of data and samples taken in an emergency situation, where confusion over samples taken during clinical care were reportedly reserved for future research without the explicit consent of the participant.

Equity: Concerns about equity can have significant political and healthcare consequences (e.g. the Indonesian government withholding samples of avian influenza). There is a need for deeper reflection on the moral claims for equity in research at a global level related to (i) rights and responsibilities related to contribution to research (ii) priority to the worse off, and (iii) equal opportunity to determine what is owed to countries during an epidemic emergency. Three specific issues of equity were raised at the meeting: access to samples and data, access to treatments, and post-trial obligations, that are tightly interwoven with countries' and communities' willingness to participate in local and international research efforts during epidemics.

Adaptive Trial Design: A panel discussed whether a randomised control trial design is the most appropriate for research during emergency epidemics. The principle of equipoise provides justification for the randomisation of some participants to placebo or standard care. However, knowledge collected during a trial is not binary but on a spectrum; it may become clear that a treatment is superior to standard care, thereby shifting the ethical imperative towards providing the experimental treatment to more participants. Also, the amount of certainty required for widespread treatment recommendations by the medical community may be different from the uncertainties that a doctor or patient might accept – especially in the context of an emergency epidemic where there are no recommended treatments. Against the backdrop of Ebola's high morbidity and mortality, the social and political acceptability of randomising to placebo/standard care emerged and, with foreign health workers prioritised for treatment, arguments around equipoise became strained.

Adaptive designs may be ethically different because the trial is altered while the study is conducted based on what is learned about the intervention allowing a higher percentage of patients to receive the possibly effective experimental treatment. Participants agreed that this does not eliminate ethical tension but significantly reduces it. Researchers continue to debate the comparative scientific value of adaptive designs.

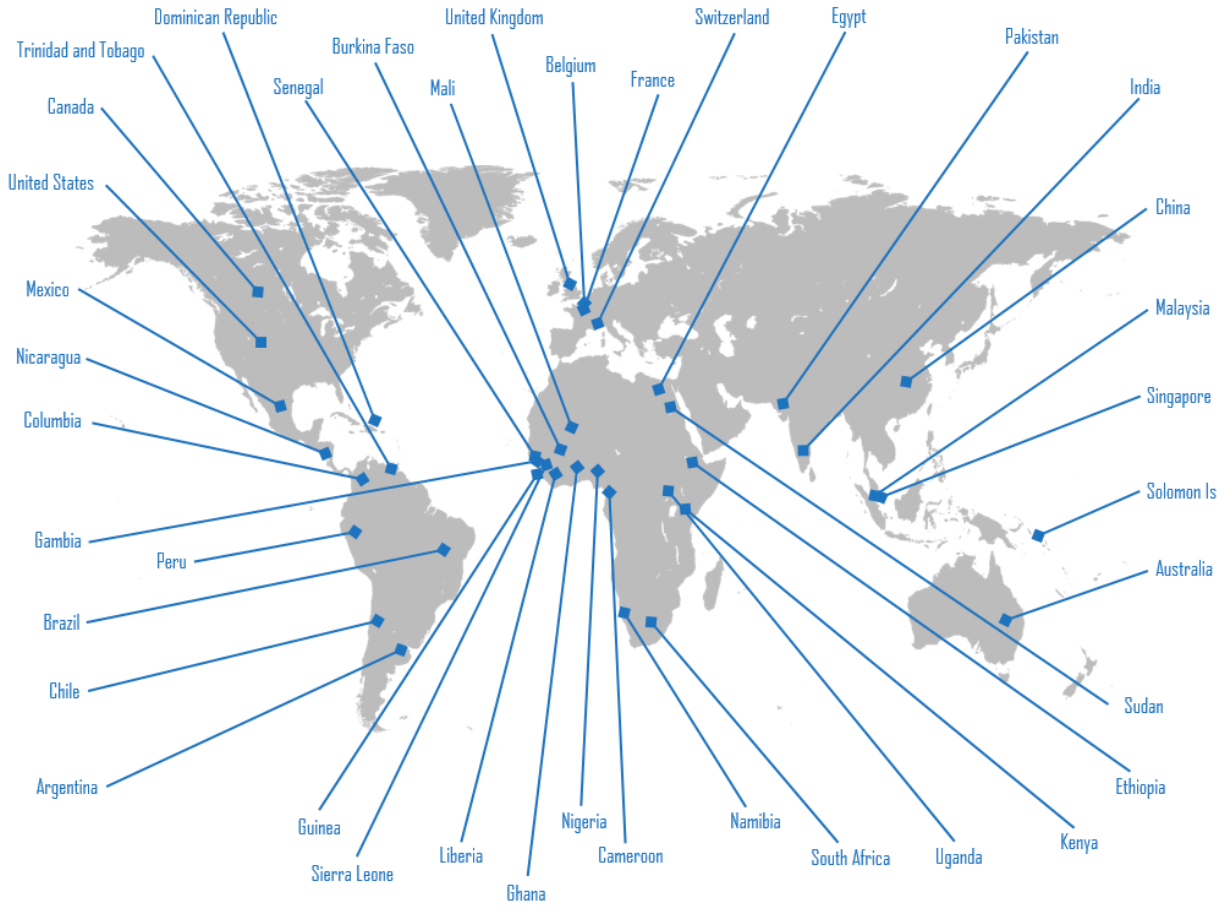
Ethical Preparedness: Research needs planning which is hard to do in an emergency context. Often, protocols cannot be developed, reviewed and initiated quickly enough and local research capacity is rarely sufficient. Substantial work is needed between epidemics to create the infrastructure, funding, processes and policies for ethical research to be implemented quickly and decisively:

- *Comprehensive international/global public health ethics guidance grounded in implementation of research in epidemic outbreaks*
- *Pre-approved standard operating procedures, protocols and mechanisms for a fast track research ethics committee approval process for common types of research proposed during epidemics*
- *Preparedness strategies for local research infrastructure and capacity building for local research expertise*
- *Capacity building for local research ethics committees*
- *Research ethics expert advice network activated for epidemics*

Summary: The meeting provided a platform for stakeholders from across the world to discuss contentious and complex ethical issues for research and helped to forge new connections between participants. Many of the key challenges addressed require substantial ongoing engagement, research and support to resolve and the GFBR meeting aimed to be a catalyst for change to ensure that good quality research can be conducted in epidemics appropriately, ethically and with the support of all communities affected.

Introduction

The Global Forum on Bioethics in Research convened at the Fondation Mérieux in Annecy, France, in November 2015, to explore the ethical issues related to "*Emerging epidemic infections and experimental medical treatments*". With experts in bioethics, epidemiology, anthropology, public policy and clinical research from over 35 countries (see map of participants' countries below), the meeting delved into pressing ethical issues for scientific research with many who had first hand experiences of infectious disease outbreaks. The meeting topic was chosen both for its timeliness in light of the recent Ebola outbreak, and the profound unresolved ethical challenges in research conducted during epidemics. The special ethical considerations that emerge when research is undertaken in humanitarian crises, including trust and consent, community engagement, ethical preparedness and international coordination, equity in research and the ethical acceptability of adaptive trial designs were examined.



Background

Participants acknowledged the special circumstances impacting ethical decision-making while conducting research during epidemics, including (i) high uncontrolled morbidity and/or mortality, (ii) scarcity of resources in many areas (including manpower, logistics, finances, basic healthcare supplies, treatments and vaccines) (iii) the need for immediate decisions on the basis of incomplete information and uncertain validity and (iv) establishing a moral compass for decision-makers. Although guidance and frameworks for undertaking research in emergency settings do exist, putting the principles of ethical research conduct into practice in an epidemic situation remains an extremely challenging task. The meeting used a series of case studies submitted by participants with close experience of conducting research in disease outbreaks, primarily from low- and middle-income countries which ensured that discussions about complex ethical issues remained grounded in the practical realities of how research was conducted.

The keynote presenter contextualized key issues within a historical discourse on epidemics noting that lessons learned from the previous epidemic are rarely remembered. Populations affected by epidemics have been stigmatised, isolated and fearfully perceived as 'other'. Social and economic disruption creates significant challenges for basic health infrastructure, public health responses and the political environment, which has to accommodate an often competing range of interests. Throughout the meeting the need for a clear and cogent ethical justification for any research undertaken in these emergency situations was expressed.

1. Trust and context

Trust in the context of research, in particular in an emergency epidemic situation, is multi-factorial, fragile and often lacking. Trust is essential for research if it is to achieve its purpose as a social good but how to build and maintain it during a humanitarian crisis is both challenging and complex. It is not only a question of a participant's trust in research and researchers (e.g. demonstrated by their confidence that the researcher will act with integrity, in the participants' and publics' interests and within the appropriate legal or institutional requirements) but also trust at the community, inter-institutional, intergovernmental and international level.

What inhibits or predicts trust?

In an epidemic outbreak situation there is often a background condition of distrust. The very nature of an outbreak disrupts normal social and economic relationships, leading to profound uncertainty and fear within communities. **Case study 5** emphasised the importance of understanding the historical context of the affected regions in the recent Ebola outbreak: civil disruptions left political systems fragile with citizens sensitive to signals of marginalization and distrusting of governments. A history of distrust of foreign nationals was promulgated by the governments following the incursion of foreigners into domestic politics during humanitarian and refugee programs that followed the period of civil crisis.

Case study 5: ***History, culture, social norms and Ebola drug and vaccine research in Ebola affected regions***

Amuni Yakubu, Federal Ministry of Health, Nigeria, on behalf of Morenike Folayan, Awolowo University

The management of Ebola has made it necessary for western scientific thinking to confront the realities of other cultures. In communities affected by Ebola, research is a form of partnership between communities and researchers with the aim of achieving better health. Socio-cultural practices and understandings validate or invalidate the practice of science and how community members make sense of the clinical trial process. Unfortunately, there has been little discussion about the realities of the history, culture and social norms of the people of Sierra Leone, Liberia and Guinea, and the ethical imperative to take into consideration these issues in the design and implementation of Ebola drug and vaccine clinical trials.

What makes researchers and research trustworthy?

Responsibility for engendering trust falls across the broad spectrum of actors in the research enterprise, including governments, international organisations, researchers and research ethics committees. The mechanisms for developing trust may be distinct but they are mutually reliant. For example, researcher community engagement can help to build trust but this is unlikely to succeed if there's a lack of confidence in the systems governing research.

Participants discussed ways in which distrust could potentially be overcome in these circumstances, reaching the following points of consensus:

- **Understand local perceptions of research and researchers:** A communication (and engagement) plan should be an integral feature of the initial research design process.
- **Continuous communication and transparency:** Researchers should ensure that communities are adequately informed about the key research concepts as well as the process of review for scientific and ethical merit of the research i.e. approved by an independent ethics review committee with a good record of abiding by ethics guidelines.
- **Accountability:** Highly accessible systems of accountability should be established to promote confidence in the research process by providing continuity, assurance and defined lines of responsibility.
- **Understand local context (political institutions and local power dynamics):** The involvement of local expertise was seen as an effective way to counter tensions regarding foreign researchers and as a means to build research and ethical capacity locally.

Community engagement and anthropological research can help inform these efforts.

Research needs a foundational planning which is very hard to do in an emergency context. Often, protocols cannot be developed and implemented quickly enough and local research capacity is rarely sufficient. Complementary skills and scientific expertise from an outside country can be valuable. Ideally a researcher who is new to a community would not simply parachute in/out but instead would engage to find the community's needs and work to identify their concerns and perceptions about the planned research.

Trustworthy organizations: In an emergency situation many different organisations are mobilised and their differing roles and reputations can create a confusing, untrusting situation for the communities affected. **Case study 1** drew on a researcher's experience with Médecins Sans Frontières (MSF), an organisation known by the countries affected by Ebola from previous humanitarian work. Researchers from an organization (such as MSF) on the ground may vary over time but it can build a trusted and trustworthy reputation in a community through long term involvement.

Case study 1: ***The ethical challenges of conducting anthropological fieldwork during an Ebola outbreak: a case study from Monrovia, Liberia***

Emilie Venables, Médecins Sans Frontières

Anthropological fieldwork has played a large role in the recent Ebola intervention across the West African region, and learning about the socio-cultural context has helped to provide appropriate information and health-care services. MSF anthropologists working in Monrovia conducted qualitative research on funeral and burial practices, local perceptions on clinical trials and beliefs and perceptions around the Ebola virus and treatment. Anthropological research is essential in such outbreak situations but is not without ethical challenges.

Research ethics committees: **Case study 1** described how MSF anthropologists undertook open engagement with local and international research ethics committees on their research protocol development during the Ebola crisis; this built trust by making the ethical review process iterative and inclusive. **Action is needed to enhance the visibility and credibility of research ethics committees within the community to provide assurance that human subject research is conducted ethically**. A useful starting point would be to improve the perception by researchers of ethics review committees as a "necessary burden" to a partner and facilitator of ethical research. Professionalization may also bolstering the role and reputation of research ethics committees.

Research communication: **Case study 4** described the impact of a high-profile objection by the Ghana Academy of Arts and Sciences to a Phase 1 clinical trial of an Ebola vaccine in Ghana, despite approval by the National Research Ethics Committee. Subsequent news stories heightened fears about the risks associated with Ebola, creating significant public concern about the ethical acceptability of conducting this research despite previous positive public response, in particular, in communities where the researchers had a good local reputation and trust. As a result, sponsors of research are now reluctant to work in Ghana. While this was a politically complex case, **it demonstrated the need to boost capacity for responsible health reporting to ensure that trust in research is not easily lost**.

Case study 4: ***Country experience on clinical trials oversight and ethical clearance in Ghana***

Ama Edwin, Korle Bu Teaching Hospital

A series of complex political challenges disrupted a planned Phase 1 clinical trial of an Ebola vaccine in Ghana earlier this year. The Ghana Academy of Arts and Sciences objected to the trial despite it having been approved by the National Research Ethics Committee through a well-established process. Fears about the risks associated with Ebola created a significant and public conflict in views over the ethical acceptability of conducting research in these circumstances.

Consent: Researchers in the field during epidemic outbreaks reported challenges to their consent process with:

- Quarantined participants
- Proxy consent when participants are incapacitated
- Involvement of children in research when parents are absent

The point was strongly made that these were not just "cultural" issues. Video footage circulated during the Ebola epidemic was presented showing a patient who escaped from isolation being rounded up by health care workers wearing personal protective equipment, amidst shouting crowds. The question of whether "free" consent can be given under "coercive" conditions must be considered.

Therapeutic misconception: In the midst of an epidemic of an untreatable infection, it is extremely difficult for participants to avoid therapeutic misconceptions – any experimental treatment, even if untested, may be thought of as a potential miracle cure and the opportunity to enrol in a trial is the only option for care where there was previously none. Due to this issue, disagreement was expressed on whether ethically, research can be conducted during an epidemic emergency. In a clinical setting it might be ethical to offer untried medicines when people genuinely have no other options and the alternative is death. However, it may be a highly problematic type of opportunism – using the opportunity of an epidemic to test a potentially therapeutic agent. It was argued that research could start once the epidemic is under control, however, who should judge when the appropriate time has come?[1] Others expressed the view that research does not need to be set up in opposition to clinical care (e.g. standard care given with therapeutic use monitored). Some attendees offered anecdotal evidence that some patients recognised the solidarity of participating in research when they or their family have benefited from drugs that have been developed thanks to other patients taking the risk and participating in a trial before them.

Broad consent: Disagreement was also expressed on the question of broad consent for future use of data and samples taken in an emergency situation. In the context of the Ebola outbreak, there was reportedly heightened confusion over samples being taken for clinical care which were then reserved for future research without the explicit consent of the participant.

[1] Also, this approach raises a question as to whether enough research participants could be enrolled in the study for it be to scientifically valid. See 'As Ebola epidemic draws to a close, a thin scientific harvest' Cohen, J. and Enserink, M. Science 351 (6268): 12-3 (2016)

2. Community engagement

Approaches to community engagement need to respond to the implicit tension between research and public health activities and for researchers to understand that their 'message' will be one of many voices. Further, researchers must accommodate the different levels of approval that might apply and tailor engagement accordingly e.g. authorization (e.g. at regulatory level), permission (at community level), consent/assent (at an individual level).

It is likely in an emergency context that researchers will not have the luxury of time or pre-existing structures in the affected, under-resourced countries to organize effective community engagement. Epidemic, emergency situations involve a unique set of conditions that create a challenging backdrop for community engagement:

- **Time and a fast changing landscape:** Time will be critically important to employ public health measures, resulting in limited opportunities for up-front engagement highlighting the need for community engagement strategies to be quickly operationalized.
- **Public sensitivities and vulnerability:** Epidemic situations will likely give rise to feelings of vulnerability, desperation, fear (e.g. of disease, stigmatization, isolation) and suspicion, which need to be taken into account when deciding how, with whom and when community engagement should take place.
- **Potential for confusion:** Engagement efforts need to be cognizant of the increased potential for blurring messages regarding the provision of health care and research processes.
- **Experimental treatments:** Experimental treatments available to test against rare epidemic infections may be underpinned by less evidence than usual for normal therapeutic intervention trials presenting additional challenge to communicating this uncertainty during engagement.

Case study 1 provided an example of qualitative research conducted in Monrovia at the time of the Ebola outbreak, investigating funeral and burial practices, local perceptions of clinical trials and beliefs and perceptions around the Ebola virus and treatment in order to provide appropriate information and healthcare services to various stakeholders.

Engaging different stakeholders: The range of stakeholders in an emergency epidemic situation will likely be different and larger than a routine clinical research environment (e.g. with heightened public sensitivity there may be vested interests at the institutional and/or political level).

Pragmatically, the researchers have to start engagement somewhere; if there are no established networks or local credibility, someone the community is likely to trust is approached. However, many delegates cautioned that researchers may not reach peripheral members of the community if engagement relies on leaders. Indeed, in the experience of some delegates, community leaders have created a bottleneck with influential men at the top, and people in the community being scared to criticise or question them.

Case study 2 focused on the KEMRI Wellcome Trust Research Programme which provides a good example of how such engagement can be done well when the long term community research structures and practices are in place.

Case study 2: ***Case study of best practices in community engagement adapted for an Ebola phase 1 study***

Patricia Njuguna & Maureen Njue, KEMRI Wellcome Trust Research Programme

The Kilifi research programme has an elaborate Community Engagement strategy which was developed to strengthen mutual understanding between the research programme and key stakeholders. In this case study, we discuss the community engagement model for the recent Ebola phase 1 trial in Kilifi, Kenya, the ethical challenges faced and 'best practices' adopted for this trial.

Trust and community engagement: Community engagement cannot easily resolve long term distrust of authority, the impact of 'foreign' research on community relations, stigmatization of survivors (**case study 3**) and distrust if one neighbourhood has information or access to resources where others don't. Ebola vaccine trials in Guinea and Sierra Leona addressed some of these issues by first vaccinating the coordinator of the national Ebola response and other people in significant positions. Press conferences with updates to say how the vaccine was affecting the coordinators were held to build trust in the vaccine research.

Case study 3: ***Bonglam Kromah, physician's assistant: using convalescent blood from Ebola survivors***

Jennyfer Ambe, Global Emerging Pathogens Treatment Consortium, and Godfrey Tangwa, University of Yaounde, Cameroon

This case study describes the experiences of a healthcare worker in Liberia who survived Ebola Virus Disease (EVD). Along with a outlining a range of difficult ethical challenges about how he was treated socially and by the health system, it poses the question: once he had recovered, could he ethically be recruited into a clinical study or donate blood in attempt to save the life of another EVD patient?

Research projects often employ staff drawn from the community matched in cultural and linguistic characteristics to research participants, not only to help with the practical issues but also to help build trust. However, experience from one of the Wellcome Trust African Units showed that using local people to communicate with the local community made the community suspicious: they questioned why the scientists wouldn't come out and talk themselves. This speaks to the need for an evidence base to design specific strategies of engagement for specific communities and circumstances.

3. Ethical preparedness and international coordination

Given the substantial time pressure on research protocol design, planning, engagement and undertaking the research itself in an epidemic situation, there was consensus that substantial work is needed between epidemics to create the infrastructure, funding, processes and policies ready to act quickly and decisively:

- **Policies and guidance:** Despite the existence of ethics guidance in relation to specific diseases (e.g. pandemic flu, TB and HIV) comprehensive international/global public health ethics guidance related to epidemic outbreaks is lacking. (See below)

- **Pre-approved standard operating procedures, protocols and mechanisms for a fast track research ethics committee approval process:** International research organizations such as WHO could hold a set of pre-approved standardised protocols for emergency situations. This might help promote trust between researchers and research ethics committees, understanding that any final approvals would still be at the local level.
- **Infrastructures – both public health and research:** In order to conduct ethical research related to public health emergencies, preparedness strategies should include maintaining research facilities, mechanisms for quick release of funds when an epidemic occurs and mechanisms for channelling funding to meet specific epidemic needs.
- **Capacity building for local research expertise (see Section on Equity)**
- **Capacity building for research ethics committees:** Including, for example, education on different trial designs and consent issues specific to the context of an emergency epidemic, along with the preparation of processes/templates for use in these settings.
- **Ethics advice:** Define the role for ethicists in the field who could provide researchers with advice in real time and support the flexible decision-making process that is required in an epidemic. Alternatively, WHO could convene a group of ethicists to advise in these circumstances (see more below).

Case study 4 provided a stark example of how a complex political environment can disrupt research conducted in emergency situations. This case study made clear that a lack of clarity over who has authority for research approvals can cause difficulties and confusion: clear accountability and lines of responsibility, set out and agreed upon outside of time-pressed situations, are essential.

Role for WHO: During the epidemic Guinea requested an Ebola trial to be based in the country. WHO was represented in talks with trials coordinators when this matter was discussed. As no other organisation was willing to take on the liability of a trial in Guinea, WHO stepped in. WHO had been directly involved in research before but this was the biggest project to date. Some meeting participants expressed concerned at what they considered to be a high conflict of interest, given WHO's role to set the guidelines by which researches should operate. Others noted that this was not solely a 'WHO trial', as around 20 organisations were involved in the study. Whether or not there was a conflict of interest in this case, it was agreed that greater transparency at the time of decision-making would have been welcomed.

The WHO is working to develop ethical guidance for public health response to epidemics, involving the synthesis of 24 existing guidance documents (including 8 on Ebola). Existing guidance tends to be addressed at a very high level and without a clear sense of how to implement it in concrete situations. WHO aims to develop an implementation guide with concrete case examples of how principles were applied in specific situations.[2]

Further practical measures were proposed during the discussion including the development of:

- **A typology of epidemics** (e.g. whether air borne, contact only or vector borne; whether death is quick or slow; and morbidity and mortality etc.) that would be helpful in applying ethical guidance.
- **A typology of methods for community engagement**, differentiating between non-emergency and emergency settings and potentially drawing on the Good Participatory Practice Guidelines.

[2] The results of this work (which includes the identification of case studies and development of checklists) will go out for peer review in January 2016.

- **A rapid response team** charged to give tailor-made, *de novo* ethics advice.
- **Training programmes for research ethics committees** in the specifics of research in emergency epidemic situations.

4. Equity in research

Concerns about equity can have significant political and healthcare consequences, as evidenced by the case of the Indonesian government withholding samples of avian influenza, described in **case study 6**. When the H5N1 virus hit Indonesia in 2005, initial cooperation by the Indonesian government with international research efforts turned to refusal to share further samples, because of pharmaceutical access to develop vaccines that would only be commercially available. The Indonesian government described the international sample sharing and surveillance system as 'imperialist'.

Case study 6: *H5N1: Flu vaccine supply for those who contribute to seed stock*

Voo Teck Chuan, National University of Singapore

During the H5N1 influenza outbreak, Indonesia sent virus specimens to a World Health Organisation influenza collaborating center. It later emerged that a pharmaceutical company was allowed access to the samples to commercially produce a vaccine, which it subsequently tried to sell to the Indonesian government. This case highlighted how the disparity of resources and power imbalances contributed to different perspectives regarding global public health surveillance, data sharing, and the fair distribution of benefit and burden.

Meeting participants agreed that because epidemics know no borders, there is a need for global assessment and global leadership on the questions of equity in research during epidemics. While various international mechanisms (e.g. CIOMS guidelines) that address equity exist, there is a need to have a deeper reflection on the moral claims for equity in research at a global level related to (a) contribution, (b) priority to the worse off, and (c) equal opportunity to determine what is owed to countries during an epidemic emergency. It was acknowledged that there is still lack of clarity about what exactly the principle of justice requires in specific epidemic situations.

Three specific issues of equity were raised: access to samples and data, access to treatments, and post-trial obligations. These issues are tightly interwoven with regard to countries' and communities' willingness to participate in local and international research efforts during epidemics. Questions about the use of samples by the international research community, for example, should not be isolated from other issues around vaccine development, researcher obligations to communities, scientific capacity building, publication rights, different countries' healthcare needs, post-trial access and public health surveillance obligations.

Access to samples and data: Concerns arose over sample sharing in West Africa when researchers planned to ship Ebola samples out of the region as there was no capacity to store and analyse the samples in a regional biobank. Scientists focused on critical research questions and the urgency of sample analysis did not necessarily consider whether the situation offered an opportunity to develop biobanking capacity in the region. Countries

may understandably appeal to 'viral sovereignty' to retain control over samples found within their borders if there is not a fair and equitable framework in place agreed and adhered to by all stakeholders.
In an emergency situation, there is an urgent need to share data quickly and widely in order to inform public health decision-making. However, there is a question about whether it is ethical to put data into the public domain when it could be incomplete, potentially of poor quality and could be subject to revision. For example, in the Ebola outbreak, some models predicted an exponential rise in case load, on the basis of early real time data, which turned out to wildly overestimate the progression of the disease. Raw or unanalysed data often requires significant expertise and software to interpret and interrogate accurately that may not be available to local researchers without outside support. Without the building of local research capacity, scientists will be reliant on external expertise to access and make sense of the data collected, which exposes them to the risk of being 'scooped' in their analyses.

Access to treatment: An international 'Pandemic Influenza Preparedness' framework was developed in 2011 in response to the Indonesia situation, urging vaccine manufacturers to reserve small quantities of vaccine for use by developing countries. It is agreed that capacity to buy cannot be the criterion to decide who has access to what is needed during an epidemic, however, it remains unclear what the relation should be between contributions to research and access to subsequently developed treatments or vaccines.

As described in **case study 7**, public health officials in Kerala, India faced an epidemic of a viral tick-borne disease with no effective treatment. With limited supplies of a vaccine, of questionable efficacy, it was a challenge to decide whether to administer it compared to an experimental intervention and who to vaccinate first: forest workers or the local tribal populations. The nearest hospital was unaffordable for the tribal populations. While the meeting participants agreed that any intervention should be given based on greatest need, some argued that the experimental intervention should have been undertaken only as part of a trial with data collected on a scientific basis, in order to ensure knowledge was gained about the efficacy of the vaccine. This challenged a previously articulated argument regarding the Ebola epidemic that it is ethical to provide an unproven treatment if there is no alternative but only as part of clinical care, not in the context of a research study.

Case study 7: ***An emerging disease – KFD – strikes a tribal district in Kerala for the first time***

Jayakrishnan Thavody, Government Medical College Kozhikode

Kayasanur Forest Disease (KFD) is a tick-borne viral disease. KFD appeared in a district of Kerala state in January 2015 among tribal populations and forest department staff. With limited supply of a vaccine, the efficacy of which has not been established, there was a dilemma about whether vulnerable populations should receive the vaccine, and if so who should receive the vaccine first.

While it's widely recognised that a country has obligation to help its citizens, there was consensus at the forum that during the Ebola epidemic people were uneasy about foreign health workers being helicoptered out for treatment, viewing this as detrimental to community relations. It was also recognised that equity might require that therapeutic options should be prioritized based on criteria to maximize benefits. In practice, that might mean prioritizing treatment for health care workers, whose health is the key to providing health care to others,

and who are at greater risk due to their role. There should be transparent principles and processes by which decisions for the allocation of treatment are made, in particular in relation to foreign health workers.

Post-trial researcher obligations: Participants discussed what bearing the contribution of specific populations to the research endeavour should have on access to developed treatments after the trial, but no clear principles of consensus emerged.

5. Adaptive trial design

A panel discussed whether a randomised control trial (RCT) design is the most appropriate for research during emergency epidemics where the situation is both complex and evolving and where data are required urgently to inform treatment choices. Compelling arguments were presented that adaptive trial designs have the capacity to yield meaningful and interpretable data quickly and that these might be considered as preferable (although recognized that such designs are more complex to coordinate among sites).

RCTs are not without ethical tensions, including as between a doctor's duties to the individual patient verses the need to improve care for future patients and between deontological duties verses utilitarian commitments. The principle of equipoise provides an ethical basis for RCTs, specifically, a justification for the randomisation of some participants to placebo or standard care. Panelists identified problems with this approach: first, knowledge collected during a trial is not binary but on a spectrum; at some stage it may become clear that a treatment is superior to standard care, thereby shifting the ethical imperative towards providing treatment to more participants. Secondly, the amount of certainty required for widespread treatment recommendations by the medical community may be different from the uncertainties that a doctor or patient might accept – especially in the context of an emergency epidemic where there are no recommended treatments. It was against the backdrop of Ebola's high morbidity and mortality that the social and political acceptability of randomising to placebo/standard care emerged and, with foreign health workers prioritised for treatment, arguments around equipoise became strained.

Adaptive designs may be considered to be ethically different because the trial design is altered while the study is being conducted, based on what is learned about the intervention. A much higher percentage of patients receive some kind of treatment and study arms are dropped if interim analysis shows another arm is better. In all cases, therefore, fewer patients are assigned to an arm that is believed "currently" to be the inferior arm and there is a commitment to learning throughout the trial. These factors do not eliminate ethical tension but significantly reduce it.

Although there is debate within the scientific community regarding the comparative scientific value of adaptive designs[3], forum participants appeared to be united in the view that emergency epidemic situations require flexibility in how trials are designed that is ethically and practically acceptable to the community in which the research is to be conducted.

The potential for expanding research methodologies in the context of an epidemic was recognised by the WHO Ethics Working Group when they concluded that 'all scientifically recognized methodologies and study designs

[3] 'As Ebola epidemic draws to a close, a thin scientific harvest' Cohen, J. and Enserink, M. Science 351 (6268): 12-3 (2016)

should be considered as ethically acceptable'.[4] And similarly, the Presidential Commission for the Study of Bioethical Issues in its report on Ethics and Ebola concluded that 'no one clinical trials design is ethically required in the context of the current Ebola epidemic'.[5]

Forum participants recognised a clear need for education and capacity building in this area for both local scientists and research ethics committees so they are prepared for decision-making in crisis situations. One proposal was for the WHO to co-ordinate this training and to create a methodology and ethics panel to advise both RECs and researchers on adaptive trial design.

6. Outcomes to take forward

In the concluding session of the meeting, a summary of the work that should follow from the two-day meeting was presented:

- **Conceptual work:** it is clear that key ethical principles are valuable in the context of epidemics, but that questions around issues of justice, equity and emergency research vs compassionate care and the balance between individual and collective interests require further conceptual work.
- **Empirical work:** the discussion revealed a wide range of experiences and practices from across the world, with very different perspectives. Empirical work to understand the views of different stakeholders would be valuable in mapping where the tensions lie so that in anticipation of future outbreaks, key points of contention could be quickly identified. Empirical work assessing different types of trial design in non-emergency contexts would also be extremely useful to establish whether and how adaptive designs are a suitable, robust methodology.
- **For policy and practice:** inter-epidemic preparedness is vitally important for policy and research practice. Template standard operating procedures for RECs and other review groups could help speed up review in emergency situations whilst ensuring robustness, alongside generic protocols and templates for trial designs that can be quickly mobilised. Continuing work with the WHO on developing clearly implementable guidelines that can be applied in practice will be highly valuable.

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[4] 'Ethical issues related to study design for trials on therapeutics for Ebola Virus Disease' WHO Ethics Working Group Meeting – Summary of discussion (20-21 October 2014)

[5] 'Ethics and Ebola: Public Health Planning and Response' Presidential Commission for the Study of Bioethical Issues. February 2015