NUFFIELD COUNCIL ON BIOETHICS

Research in global health emergencies: ethical issues

Call for evidence

Introduction

The Nuffield Council on Bioethics has established a working group to investigate the ethical issues arising in research in global health emergencies. Recent emergencies, in particular the 2014-16 Ebola epidemic in West Africa and the current outbreak in the Democratic Republic of the Congo, have highlighted the important role of health-related research in outbreak and humanitarian response. However, the current lack of consensus on what is ethically acceptable during emergencies has both impeded the progress of valuable research, and added to the risk that research might be carried out in unethical ways.

The aim of this project is to help develop a common understanding of what constitutes ethical research and research ethics in such circumstances, and, where appropriate, to make practical recommendations for change. It is concerned not only with the traditional 'research ethics' questions of study design, review, and recruitment, but also with the inherently ethical questions of imbalances of power and influence, and the duties and responsibilities of the many stakeholders concerned in funding, facilitating, reviewing, conducting, and reporting research. Those with an interest in this project thus include: potential research participants and their families; researchers and research institutions; healthcare practitioners, other humanitarian responders, and the agencies for whom they work; funders; editors and publishers; national and international policy makers; research ethics committees; regulatory agencies; and training institutions.

We are very much hoping for contributions to this call for evidence from a diverse range of respondents, drawing on their direct experience in emergency response and / or on academic work in this field. These will play an important part in influencing this project and its final recommendations. Please feel free to respond to as many, or as few, of the questions as you wish. Each section includes a brief explanatory section and several questions, with optional links to further commentary and references.

Read more: introduction

1. What constitutes a 'global health emergency'?

Examples of global health emergencies potentially within the scope of this inquiry

- Major outbreaks of infectious disease where there is currently no effective treatment or vaccine: for example the 2018 outbreaks of Lassa fever in Nigeria, Nipah in India, and Ebola in the DRC
- Physical and mental health impacts on civilians in conflict zones: for example in Syria, Yemen, Myanmar, DRC, Ukraine
- The provision of health care for displaced persons: for example in refugee settlements in Lebanon
- Health impacts of natural and human-induced disasters such as the 2010 Haiti earthquake; the 2011 Fukushima nuclear accident in the aftermath of earthquake and tsunami; and typhoon Haiyan in 2013

There is no single agreed definition of a 'global health emergency', or indeed of the related concepts of a 'public health emergency of international concern' or of a 'global health threat': various definitions are used for different purposes. For the purposes of this project, we are concerned with identifying those threats to public health that have the capacity to have global impact, and that may potentially challenge standard approaches to research ethics. Such threats are associated with 'radically non-ideal circumstances' in which to conduct research; where, at the same time, research may play an important role in achieving an effective response, both now and in the future. We recognise that there are a number of major threats to public health at a global level that fall outside this definition (for example, the increasing health burden of non-communicable diseases), on the basis that their nature does not challenge current research norms in this way. Our working definition should not be seen as categorising these global health threats as being more or less significant, or deserving of resources.

We suggest that for the purposes of this inquiry, a global health emergency is characterised by the following features:

- It is triggered by a **disruptive shock** – a sudden and significant change from the ordinary course of events.
- This disruption entails **risks of significant harm to health** both for individuals, and at population level.
- The effectiveness of the response is directly linked to the **timeliness** with which the response is undertaken.
- The health threat **may extend beyond national borders and is a matter of regional and international concern**: this may be in terms of the potential for direct impact on other countries and / or in the need for an international element in the response.
- There are **barriers hindering effective response**, for example in terms of scientific uncertainty, availability of resources, or disrupted infrastructure.

Read more: what constitutes a 'global health emergency'?

Questions 1 and 2

1. **Please comment on this working definition of a global health emergency.**

2. **What might be the ethical implications of defining global health emergencies in this (or other) ways?**

2. Undertaking research in a global health emergency: whose voices should be heard?

The ethical conduct of research relies not simply on the detail of a particular study and the way in which it is carried out, but critically on broader structural issues of power and influence that shape the whole research endeavour – from the inception of research to the communication and implementation of any post-research findings. The question of *who* is 'at the table' when significant decisions are made, and the relative influence of those voices, arises throughout the research process, and in the context of many different relationships. These issues arise, for example, in the context of scientific leadership; in the role and influence of policy-makers and funders; in engagement with affected communities and community structures; and in interactions between research ethics committees in different countries.

The importance of research priorities being shaped by domestic policy is widely recognised, as is active engagement with communities from whom participants may be drawn. However, this creates particular challenges in a rapidly unfolding emergency, at the level of both professional and community relationships. Moreover, who 'represents' a particular community may be unclear. There may be multiple communities involved at a local level, with different leadership structures, perspectives and values. Because of regional or other differences, national governments may not be perceived as speaking for particular populations. Indeed, the nature of the emergency may lead to 'communities' being artificially created, for example through displacement.

Read more: undertaking research in a global health emergency: whose voices should be heard?

Questions 3–5

3. **Please provide examples of how, despite the urgency and pressure of other aspects of immediate humanitarian response, national governments, local researchers, and affected populations have genuinely been 'at the table' in setting research priorities in a global health emergency.**

4. **Please comment on what you believe are the essential aspects of community engagement in an emergency, their ethical justification, and how these can they be achieved.**

5. **Are there *any* circumstances in which research might be so important, and time so short, that this could outweigh the need for local voices to be heard?**

3. Study design and review

The features of a global health emergency, identified in **section 1**, pose a number of major challenges for both the design, and then the review, of research proposals. Throughout the process of prioritising, designing, and reviewing a particular study, decisions may have to be made within very tight timeframes in the knowledge that delay in moving forward also carries risk: decisions, for example, as to what constitutes an acceptable balance of risk and potential benefit, in a context of considerable scientific uncertainty. The contextual risks (both physical and non-physical) to which populations are exposed, and which may affect consideration of balance of risks and benefits of study participation, may also not be well understood, especially by non-local researchers and reviewers. These include risks of stigma associated with local attitudes to disease or research, or inadvertent loss of confidentiality through the very fact of research participation. Importantly, the risk of *exclusion* from research may also be overlooked, especially where studies offer access to potential benefits (financial or non-financial) that are otherwise unavailable to the population (see also **section 5**).

The 2014-16 Ebola outbreak in West Africa brought to the fore debates about the ethical acceptability of novel trial designs. These include:

- 'cluster' randomised trials, where it is groups or clusters (such as health centres or villages), rather than individuals, that are randomly assigned to an intervention;
- 'stepped wedge' designs, where an intervention is allocated sequentially to study participants or to clusters (as, for example, in the 2015 Ebola ring vaccination trial where the clusters of contacts of infected persons were randomly assigned to immediate or delayed vaccination);
- 'adaptive' designs in which allocation to study arms (or indeed the study arms themselves) changes throughout the study in response to emerging results.

An expert panel convened by WHO also approved the "monitored emergency use of unregistered and experimental interventions": that is, the use of such interventions outside the framework of any kind of clinical trial. Despite considerable work in this area in the intervening time, there remains a lack of consensus as to the circumstances in which particular designs are acceptable, or indeed whether this can be determined without reference to the specific context for which they are proposed.

Global health emergencies also pose unique challenges to the functioning of research ethics committees, particularly where these are already under-resourced and / or disrupted by the nature of the emergency. In addition to the pressure of responding flexibly and within tight timescales, research ethics committees may also be faced with sudden increases in the number of protocols being presented for review, and trial designs that are unfamiliar to committee members. Proposed approaches such as 'pre-approval' or 'pre-review' of aspects of protocols as part of emergency planning, and joint multi-country review committees, might help respond to capacity concerns, but bring their own risks of loss of local ownership and trust.

Read more: study design and review

Questions 6–10

6. **In your view, in what ways, if at all, should decisions about study design and acceptable risk be affected by the fact that the research will be taking place in a global health emergency? On what basis would you justify any variation?**

7. **In what ways, if at all, could it be morally justifiable to change the 'standard' ethical and regulatory review processes to respond to the time pressures inherent in a global health emergency?**

8. **If any differences in approach to study design or review can be justified because of the features of a global health emergency, would safeguards, such as an independent declaration that 'emergency' criteria have been met, be necessary?**

9. **When choosing a study design, is it ever justifiable to prioritise a design that will maximise knowledge and hence scope for benefit for future generations, over a design that maximises the possibility of benefit for people affected by the current emergency; or could this never be justified? On what ethical basis would you justify such a choice?**

10. **Are there any specific kinds of research or innovation that, in your view, raise distinct ethical questions and / or might demand differential ethical treatment?**

4. Making decisions about participation in research

It is widely recognised that participation in research should be based on the 'informed consent' of the participant. Researchers should assure themselves that the potential participant is competent to make a decision about whether or not to take part; that they have sufficient information on which to base a decision; and that they are acting freely, without undue pressure from others (while recognising the legitimate role of discussion with those close to the person).

Where potential participants are unable to give consent for themselves, the Declaration of Helsinki states that this may be provided by a "legally authorised representative", where this is allowed for by domestic law (including by those with parental responsibility in the case of children). In some contexts, it may also be appropriate to seek permission from community leaders before approaching individuals and their families about possible participation. Exceptionally, the need for consent in advance may be waived, for example where the research relates to treatment in an accident or other kind of emergency. The 'secondary use' of aggregated and anonymised data may also, in some circumstances, be permitted without explicit consent.

During a global health emergency, the conditions in which potential participants, their families, and communities make decisions about taking part in research are far from ideal. Factors such as disruption, panic, displacement, difficult material circumstances, and lack of access to necessary services may have profound effects on people's abilities to make free, competent, and informed choices. Family separation or quarantine may make proxy decision-making impossible for children, for adults too ill to consent for themselves, and indeed for any family members where traditionally family heads have played a strong role in decision-making. The uncertainties inherent in a rapidly evolving situation may make it difficult for any specific decisions to be truly informed.

Even in less challenging circumstances, however, it is important to recognise that consent alone is not sufficient to ensure a research study is being conducted ethically. In many circumstances, particularly in low-income environments, taking part in a study may bring benefits, such as access to qualified healthcare professionals, that cannot be obtained in other ways; and people are very unlikely to refuse to take part. Other protections, such as independent scrutiny of the social value of the proposed research to local populations, and of the likely risks and burdens involved, are thus also essential. (See also **section 3**.)

Read more: making decisions about participation in research

Questions 11–13

11. **Are you aware of any examples of when an emergency seemed to demand a different approach to making decisions about research participation? If so, please explain how any derogation from standard approaches might be ethically justified, and the relevance of the kind of research concerned (for example research involving physical intervention as opposed to research involving data only).**

12. **If we consider the giving of valid consent as *one* element in the 'ethical ecosystem' around research in emergencies, and recognise too that consent is often imperfect, what are the other essential elements of the ecosystem necessary for such decision-making to be considered legitimate?**

13. **Are there any circumstances in which participation in research should not be optional? (See also section 5, on public health)**

5. Duties at the interface of research, treatment, and public health

'Research', 'healthcare' and 'public health interventions' are often treated as quite separate activities, governed by distinct ethical and regulatory codes. Yet in practice, these boundary lines may be far from clear: interventions offered in the context of research may potentially have therapeutic effect and can be eagerly sought after for that reason; and the same personal data may be obtained from participants / the public for both research and public health purposes. Distinctions may also be hard to draw between health systems research and service evaluation or audit. There can be perverse incentives to classify such activities *not* as research, because of the way in which the ethical scrutiny of research is perceived as acting as a barrier.

In some cases, practitioners may be used to working across multiple roles: for example health professionals who regularly combine their clinical practice with a research role. In other cases, practitioners may be very comfortable in their own 'silo' and reluctant to engage with other areas of expertise and other academic and ethical approaches. Both circumstances create ethical challenges: in the first case ensuring that the demands of research do not detract from the needs of clinical care; and in the second in the obvious risks posed to collaborative working.

Such blurred boundaries, and associated ethical challenges, are particularly problematic in global health emergencies, where practitioners from many different disciplines, working for agencies with diverse approaches and aims, need to collaborate in very difficult circumstances (see also **section 7**). While the integral role of research both in achieving an effective response to an emergency and in learning for the future is increasingly recognised, there are serious practical challenges on the ground to such integration. These will often be exacerbated by shortages of personnel and other resources. In such circumstances, ethical guidance that distinguishes sharply between what is clinical care, public health, research, and evaluation may hinder, rather than support, effective co-working.

Read more: duties at the interface of research, treatment, and public health

Questions 14–17

14. **What, in your experience, are the main ethical challenges that arise as a result of uncertainties in the boundaries between treatment, research, evaluation, and public health? To what extent are these associated with logistical or resource constraints?**

15. **Is it possible to create a meaningful distinction between the collection of personal data for public health purposes, and for research purposes? What does this mean for consent and for data-sharing?**

16. **How could a more coherent approach to the complex relationships between research and other essential services in a global health emergency be developed, so that front line workers are supported by ethical guidance that reflects the realities they face?**

17. **In the alternative, do you think that there are ethical justifications for maintaining clear distinctions between the activities of ‘research’, ‘health care’ and ‘public health interventions’ in a global health emergency? If so, what are they?**

6. Obligations to / expectations of front-line research staff

In some cases, the people responsible for conducting the day-to-day work involved in a research study may be highly trained professionals, including doctors, nurses and other healthcare practitioners. In other cases, much of the direct contact with research participants will be maintained by field-workers and other front-line research staff with very variable levels of training or support. We use the term 'front-line research staff' to include all those directly interacting with research participants, whatever their professional background, and whether they are local or deployed from abroad.

A number of the features of a global health emergency, in particular its disruptive nature and the time pressure to act, combined with the nature and degree of the risks of harm, may exacerbate the ethical challenges such research staff face, compared with their work in more routine circumstances. The nature of their work may mean they are subject to stigma or other kinds of disadvantage, including, at times, risk of physical danger. Ethical dilemmas may arise in the context of their work that were not envisaged at the time of ethical review, and little, if any, support may be accessible in working out how to respond, particularly where channels of communications are disrupted or non-existent. The complex and changing situation on the ground, potentially involving many different organisations, can add to the risk of unclear lines of accountability, lack of support for both paid and volunteer staff alike, and scope for moral distress as a consequence of unresolved ethical issues in emergency contexts.

Clear guidance has been issued by bodies such as WHO and the UN's Interagency Standing Committee on the responsibilities of governments and others with respect to both locally-engaged and expatriate front-line staff. These include obligations with respect to their safety, their access to necessary training and resources, and clarity about their terms of deployment and access to healthcare. However, there remain a number of ethically-contentious issues with respect to such responsibilities. These include how and whether differential treatment between expatriate and locally-engaged staff can be justified; and how workers can best be supported when they themselves are faced with difficult ethical questions in the field.

The WHO has advised that those working in emergencies on the front-line in the healthcare sector, which may include those undertaking research, have themselves obligations to the community, including duties to participate in public health surveillance (with due respect for patient confidentiality), and to provide accurate information to the public. Recently, attention has also been drawn to the existence of abusive behaviour by some staff working for international aid agencies, and to the associated responsibilities of organisations to undertake appropriate vetting and monitoring of staff.

Read more: obligations to / expectations of front-line research staff

Questions 18–21

18. **Do the exigencies of global health emergencies (for example levels of risk, security requirements, extremity of humanitarian need, rapidity of response) change the obligations on, and expectations of, front-line research staff in any way?**

19. **What constitutes fair treatment of both local and expatriate front-line research staff, and who is responsible for ensuring that they receive such treatment? Can differential treatment ever be justified?**

20. **What mechanisms are there, or should there be, to help ensure that obligations to front-line research staff are honoured?**

21. **What ethical responsibilities do front-line research staff in emergencies themselves hold?**

7. What are the challenges of effective collaboration in global health emergencies?

Research in emergency settings is increasingly, and perhaps necessarily, collaborative and international: its success depends upon the establishment of collaborative partnerships between institutions and individuals who may have very different interests, goals, and priorities. In addition to such scientific collaboration between researchers from different institutions and countries, cooperation is also essential between those concerned with research and the many other actors in a global health emergency, such as: national and local governmental authorities and service providers; international humanitarian response organisations; intergovernmental organisations; the private sector; and the military.

Such collaboration clearly brings with it considerable practical and logistical challenges. It may also be ethically challenging, particularly in terms of how decisions made by those remote from the emergency, such as funders from high income countries, or pharmaceutical companies and their insurers, may fail to take account of realities on the ground (see also **section 2** and **section 3**). The combination of complex relationships between external stakeholders, and the remoteness of key decision-makers, may also add to the risk that local voices and local needs are not given proper attention. Military involvement may provide important logistical support both for those providing humanitarian aid and those engaged in research. However, such collaboration with the military may bring with it difficult issues for researchers in terms of how they are perceived by affected communities; in the extent to which potential participants are able to make free choices; and even in accusations of complicity in others' coercive behaviour.

The many organisations involved in response efforts may also lead to confusion and lack of accountability on the ground (see also **section 6**). Lack of clarity over the respective responsibilities of different stakeholders can lead to important interests being overlooked – in particular with respect to where responsibility lies for ensuring that local communities have fair access to any benefits of research after the emergency. Recent amendments of the Declaration of Helsinki, for example, have highlighted the importance of access to the benefits of research on the part of those communities who have contributed to that research – and the need to recognise that responsibility for ensuring such access cannot fall on researchers and research institutions alone.

Even in non-emergency settings, ensuring genuinely fair collaborations between researchers in low and high income environments may not be straightforward; and in an emergency, the challenge of ensuring local researchers are fairly involved in setting research agendas, in the process of the research itself, and in sharing its benefits, may be exacerbated. Finding effective and ethical ways of sharing data has been identified as being of particular concern: both in terms of ensuring maximum benefit for local populations at the time (through rapid data sharing to promote effective response); and in terms of fair access to data, and to associated academic recognition and authorship, by local researchers in the future. Further challenges arise in developing an ethical basis for sharing and prioritising the use of biological samples.

Read more: what are the challenges of effective collaboration in global health emergencies?

Questions 22–26

22. **Can you provide examples of where collaboration has worked well in enabling valuable research to take place in global health emergencies? What were the key success factors?**

23. **Can you give any practical examples of ways in which ethical concerns have impeded successful collaboration in research? What would have helped resolve them?**

24. **Can there be said to be an ethical obligation to work collaboratively rather than competitively in the context of global health emergencies? What might such an obligation entail and what are its limits?**

25. **What are the obligations of funders to promote collaboration in a global health emergency?**

26. **What are the key requirements for good ethical practice in sharing (a) data and (b) samples in a global health emergency?**

8. Other issues / considerations

27. Are there any other ethical issues arising in the context of research in global health emergencies that you would like to draw to the working group's attention?

Read more

Read more: introduction

Research during a global health emergency can take many different forms. Most visibly, it includes efforts towards the rapid development of new medicines and vaccines for conditions where no effective treatments or preventative measures currently exist.[1] Other areas of research include: the development of more rapid or effective diagnostic tools;[2] anthropological work seeking to improve shared understanding of local health concerns and health beliefs;[3] development and evaluation of health interventions;[4] more effective forms of surveillance to enable early identification and mitigation of health threats;[5] and research underpinning the development of effective and resilient health systems.[6] Such research is complex and difficult to conduct for a range of reasons explored in this call for evidence – not least because of the specific context in which it takes place, which may include lack of security, poor access to affected populations, uncertainty about the future, poor governance, a weakened health system, and populations in a situation of high vulnerability.

The current lack of consensus on what is ethically acceptable during emergencies and what constitutes 'good practice' is one of the factors impeding the progress of valuable research. This may also contribute to the risks of unethical practice passing undetected, of communities being exposed to research that is unlikely to provide answers to their most important questions or address their needs,[7] and to an erosion of public confidence and trust in research where it is needed most. This situation – uncertainty about what constitutes 'good ethical practice' – is likely to be further exacerbated by developments in specialist research methods, such as increasingly sophisticated sequencing methods[8] and digital health technologies,[9] and by the

---

1 See, for example, Ali A, Wahid B, Rafique S *et al.* (2017) Advances in research on Zika virus *Asian Pacific Journal of Tropical Medicine* **10(4)**: 321-31; WHO (2018) *Essential medicines and health products: Ebola*, available at: http://www.who.int/medicines/ebola-treatment/en/.

2 See, for example, WHO (2017) *New technology allows for rapid diagnosis of Ebola in the Democratic Republic of the Congo*, available at: http://www.who.int/emergencies/ebola-DRC-2017/articles/rapid-diagnosis/en/.

3 See, for example, Stellmach D, Beshar I, Bedford J *et al.* (2018) Anthropology in public health emergencies: what is anthropology good for? *BMJ Global Health* **3(2)**.

4 See, for example, Okuyama J, Funakoshi S, Tomita H *et al.* (2017) Mental health and school-based intervention among adolescent exposed to the 2011 Great East Japan Earthquake and tsunami *International Journal of Disaster Risk Reduction* **24**: 183-8. See also: Iwasa H, Suzuki Y, Shiga T *et al.* (2016) Psychometric evaluation of the Japanese version of the posttraumatic stress disorder checklist in community dwellers following the Fukushima Daiichi Nuclear Power Plant incident: the Fukushima health management survey *SAGE Open* **6(2)**: 2158244016652444.

5 See, for example, Gardy JL, and Loman NJ (2017) Towards a genomics-informed, real-time, global pathogen surveillance system *Nature Reviews Genetics* **19**: 9-20; All Africa (27 March 2018) *Nigeria: Lassa Fever outbreak slowing, but remains a concern - WHO*, available at: http://allafrica.com/stories/201803270004.html. See also: Holmes EC, Rambaut A, and Andersen KG (7 June 2018) *Pandemics: spend on surveillance, not prediction*, available at: https://www.nature.com/articles/d41586-018-05373-w.

6 Shoman H, Karafillakis E, and Rawaf S (2017) The link between the West African Ebola outbreak and health systems in Guinea, Liberia and Sierra Leone: a systematic review *Globalization and Health* **13(1)**: 1; Hanefeld J, Mayhew S, Legido-Quigley H *et al.* (2018) Towards an understanding of resilience: responding to health systems shocks *Health Policy and Planning* **33(3)**: 355-67.

7 See, for example, Ellenberg SS, Keusch GT, Babiker AG *et al.* (2017) Rigorous clinical trial design in public health emergencies is essential *Clinical Infectious Diseases*: e-published ahead of print.

8 See, for example, Gardy JL, and Loman NJ (2017) Towards a genomics-informed, real-time, global pathogen surveillance system *Nature Reviews Genetics* **19**: 9-20.

9 See, for example, Perakslis ED (2018) Using digital health to enable ethical health research in conflict and other humanitarian settings *Conflict and Health* **12(1)**: 23.

increasingly diverse collaborative partnerships and consortia required.[10] Such developments, for example, increasingly rely on access to, and transfer of, biosamples and data, attitudes to the use of which vary widely across the globe and about which there is currently significant ethical disagreement.[11]

Ethical challenges highlighted in recent emergencies include:

- lack of consensus over what constitutes ethical conduct of research in such circumstances, including the nature and scope of ethical scrutiny, acceptable trial design, participant selection, and the early release of data to help support effective response;
- different regulatory and ethical approaches within the various elements of emergency response (including humanitarian initiatives, care services and public health measures) which nevertheless need to intersect with each other, and with research activities;
- the challenges / dilemmas faced by front-line workers as a result of the close relationships between research and clinical care; and
- uncertainty over the respective roles and responsibilities of major stakeholders in establishing fair and sustainable research partnerships.

These challenges have placed limitations on the contribution that research has been able to make during emergency responses, and may result in reluctance to contribute to research. Researchers and front-line workers have been left at times to make their own decisions, unsupported, in very difficult situations. Research ethics committee members, regulatory authorities, and funders may also feel very exposed and uncertain in their decision-making, both because of the lack of consensus on what is ethically acceptable, and a lack of knowledge of the particular context. While significant work has been undertaken on a number of issues such as the ethical aspects of trial design[12] and pandemic preparedness,[13] there remains an urgent need for comprehensive ethical analysis to support an approach to future research that recognises the complex relationships between research and other essential services in global health emergencies, that builds trust between researchers and affected communities, and that facilitates collaboration and cooperation between key stakeholders. Such analysis must take into account both the scope for significant diversity in the nature of future emergencies, and in the evolving nature of the indicated research methods.[14] It must also take into account the need to take seriously both the contextual variation in ethical views and the need for shared policies across multi-country initiatives.

---

[10] As in the multiple consortia involved in the response to Zika in Latin America: https://zikalliance.tghn.org/zika-consortia/.

[11] See, for example, Bull S, Cheah PY, Denny S *et al.* (2015) Best practices for ethical sharing of individual-level health research data from low- and middle-income settings *Journal of Empirical Research on Human Research Ethics* **10(3)**: 302-13. See also: Chatham House (2018) *A guide to sharing the data and benefits of public health surveillance*, available at: https://datasharing.chathamhouse.org/.

[12] See, for example, Henao-Restrepo AM (2015) The ring vaccination trial: a novel cluster randomised controlled trial design to evaluate vaccine efficacy and effectiveness during outbreaks, with special reference to Ebola *BMJ: British Medical Journal* **351**: h3740; Global Forum on Bioethics in Research (2017) *Ethics of alternative clinical trial designs and methods in low- and middle-income country research: 28-29 November, Bangkok*, available at: https://www.wellcomeevents.org/WELLCOME/media/uploaded/EVWELLCOME/event_535/GFBR_Bangkok_summary_slides.pdf.

[13] WHO (2018) *Pandemic preparedness*, available at: http://www.who.int/influenza/preparedness/pandemic/en/; WHO (2018) *Annual review of the blueprint list of priority diseases*, available at: http://www.who.int/blueprint/en/.

[14] Flahault A, Geissbuhler A, Guessous I *et al.* (2017) Precision global health in the digital age *Swiss Medical Weekly* **147**: w14423.

The Nuffield Council working group established to explore these issues has the following terms of reference:

1. To consider, in the light of recent developments, how research may ethically be conducted in global health emergencies, and how it may most appropriately be integrated into the wider response to such emergencies.

2. To consider, in particular:

    a. the implications of the recognition that undertaking research can be an integral and necessary part of response to a global health emergency;
    b. the role of affected populations in shaping the role of research in emergency response, including recognising the potential for diverse views within those populations;
    c. the circumstances in which research activities during an emergency may offer the prospect of direct health benefit to participants, and the implications of this for ethical conduct of the research;
    d. whether there are circumstances in which the standard ethical requirements for the scrutiny and conduct of research should differ in emergencies; and if so, in what way, and with what justification;
    e. the ethical implications of the criteria for declaring a situation to constitute a 'global health emergency', and the implications for action before and after the period of the declared emergency if different ethical requirements are held to apply during emergencies; and
    f. the responsibilities of multiple stakeholders including research funders, the pharmaceutical industry and their insurers, non-profit organisations, intergovernmental bodies, and governments.

3. In considering the issues above, to take into account:

    a. the diverse nature of what might constitute a global health emergency, including disease outbreaks, natural or industrial disasters, conflict, and widespread drug resistance;
    b. the speed of innovation in research and research methods; and
    c. the nature of national obligations to assist those beyond their borders.

4. To write a report and make recommendations to improve the contribution that ethically conducted research may make to emergency response in the future.

Back to introduction

Read more: what constitutes a 'global health emergency'?

One internationally-recognised definition of a public health emergency that potentially has global impact, is that of a 'public health emergency of international concern' (PHEIC). Under the 2005 International Health Regulations (IHR), a PHEIC is "an extraordinary event which is determined, as provided in these Regulations: (i) to constitute a public health risk to other States through the international spread of disease; and (ii) to potentially require a coordinated international response".[15] The WHO suggests that this definition "implies a situation that: is serious, unusual or unexpected; carries implications for public health beyond the affected State's national border; and may require immediate international action."[16] To date, four PHEICs have been declared since the IHR rules were amended in 2005: for the H1N1 pandemic in 2009; for Ebola and polio in 2014; and for Zika in 2016.

States are required by the IHR to notify the WHO of all events in their territory that may constitute a PHEIC. If the Director General subsequently determines this to be the case, the WHO is then required to notify all other states, sharing the information it has received to enable states to respond with their own public health measures. WHO is also empowered to issue recommendations, for example with respect to appropriate health measures and travel restrictions, to offer advice and technical assistance, and to mobilize other international assistance. It can also bring into action the 'emergency use and listing procedure" (EUAL) to expedite the availability of medicines on the basis that, in an emergency, affected communities may be willing to tolerate less certainty about the efficacy and safety of products.[17]

While it is not necessary for a PHEIC to be declared for such international support to be mobilised and resources to be released,[18] in practice such a declaration may be seen as an indication of international recognition of the severity of a situation. Decisions whether or not to declare an event a PHEIC, and the timings of such declarations, have been controversial, for example with respect to whether health threats that might reach high income countries are perceived to be given greater weight.[19]

The WHO's *Strategic framework for emergency preparedness* takes a broader approach to 'emergencies'. This framework includes 'local and national' outbreaks of disease in its list of emergencies arising from natural hazards, alongside pandemics, outbreaks of pathogens with pandemic potential, and emergencies arising out of geophysical or hydrometeorological events.[20] A second category of 'human-induced hazards' includes technological hazards such as those arising from industry, and societal hazards such as armed conflict and terrorism. The impact on human health caused by these various form of emergency may be direct, and / or

---

15 WHO (2016) *International health regulations: third edition*, available at: http://apps.who.int/iris/bitstream/handle/10665/246107/9789241580496-eng.pdf;jsessionid=C1D3CAC40A62D2EB35FB106FBB78F39A?sequence=1, at page 17.

16 WHO (2005) *IHR procedures concerning public health emergencies of international concern (PHEIC)*, available at: http://www.who.int/ihr/procedures/pheic/en/.

17 WHO (2015) Emergency use assessment and listing procedure (EUAL) for candidate medicines for use in the context of a public health emergency, available at: http://www.who.int/medicines/news/EUAL-medicines_7July2015_MS.pdf.

18 See, for example, the recent response to the Ebola outbreak in the DRC, which at the time of writing had not been declared a PHEIC: WHO (18 May 2018) *Statement on the 1st meeting of the IHR Emergency Committee regarding the Ebola outbreak in 2018*, available at: http://www.who.int/news-room/detail/18-05-2018-statement-on-the-1st-meeting-of-the-ihr-emergency-committee-regarding-the-ebola-outbreak-in-2018.

19 Gostin LO (2014) Ebola: towards an international health systems fund *The Lancet* **384(9951)**: e49-e51.

20 WHO (2017) *A strategic framework for emergency preparedness*, available at: http://apps.who.int/iris/bitstream/handle/10665/254883/9789241511827-eng.pdf;jsessionid=0063EEB79F528D2D2A1446721363C3AA?sequence=1.

it may be indirect through associated disruption of health or other services. A rather different approach to the definition of an 'emergency' is taken by the UN Inter-Agency Standing Committee which refers to "a humanitarian crisis in a country, region or society, where there is total breakdown of authority … and which requires an international response that goes beyond the mandate or capacity of any single agency …".[21]

Categorisations of what constitute 'global health threats' or 'public health threats facing the world', are similarly variable. In its account of the public health challenges currently facing the world, the Independent Commission on Multilateralism, for example, first cites epidemics and pandemics, and then sets out a long list of 'other health-related challenges': these include non-communicable diseases, hunger and malnutrition, child mortality, mental health, substance abuse, road accidents, small arms and other weapons, and bioterrorism.[22] It further identifies the impact of other global trends on health, including climate change, conflict, the interface between humans and animals, and migration and displacement. In contrast, a recent review of the UK's aid response to 'global health threats' noted that in UK aid strategy such threats are interpreted as including epidemics and antimicrobial resistance, but not accidental or deliberate release of diseases, chemical and nuclear hazards, or non-communicable disease.[23]

The terms of reference of our inquiry emphasise both the wide range of circumstances in which a global health emergency might arise, and the relevance of health-related research in responding most effectively to that emergency. In developing a working definition of a 'global health emergency' for the purposes of this inquiry, we have therefore focused not on the underlying cause of the emergency, but rather on those *features* of an emergency that may potentially render the standard rules and requirements for health-related research problematic. We therefore suggest that for the purposes of this inquiry, a global health emergency is characterised by the following features:

- It is triggered by a **disruptive shock** – a sudden and significant change from the ordinary course of events. This may, but need not, be relatively short-lived: a failure to respond adequately to an emergency may mean that it is protracted.[24] Disease may itself be the disrupting factor, as in an infectious disease outbreak. Alternatively, disease or other adverse health effects may be the result of other sources of disruption: for example a natural disaster leading to a cholera outbreak or to a disrupted health system unable to deliver routine health care; widespread acute malnutrition because of famine; or conflict leading to exceptionally high levels of post-traumatic stress disorder (PTSD). Other forms of 'human-made' disaster include major food contamination and nuclear accidents. These health-related impacts of disruption may be exacerbated by wider social consequences, for example through impacts on the economy and on security.

---

21 Cited in IASC (2014) *Recommendations for conducting ethical mental health and psychosocial research in emergency settings*, available at: https://interagencystandingcommittee.org/system/files/1._iasc_recommendations_for_ethical_mhpss_research_in_emergency_settings_0.pdf, at page 9.

22 Independent Commission on Multilateralism (2017) *Global pandemics and global public health*, available at: https://www.ipinst.org/wp-content/uploads/2017/10/Global-Pandemics-and-Global-Public-Health1.pdf, pp5-7.

23 Independent Commission for Aid Impact (2018) *The UK aid response to global health threats: a learning review*, available at: https://icai.independent.gov.uk/wp-content/uploads/GHT-review_final.pdf.

24 Note, for example, that MSF has worked for decades in some countries, such as South Sudan: MSF (2014) *South Sudan conflict: violence against healthcare*, available at: https://msf.lu/sites/default/files/msf-south_sudan_conflict-violence_against_healthcare.pdf, at page 10.

- This disruption entails **risks of significant harm to health** both for individuals, and at population level. This would exclude circumstances involving minor and / or temporary health impacts, however widespread. It would also exclude risks of serious harm to individuals without wider public health consequences. In practice, the predicted seriousness of such harms may not necessarily eventuate, or the impact may not be as widespread as feared – for example because of the effectiveness of the response, or because of inevitable unknowns / uncertainties about the course of the emergency.

- The effectiveness of the response is directly linked to the **timeliness** with which the response is undertaken. This perceived imperative to act quickly may be in tension with routine elements of good ethical research practice, such as appropriate community engagement, a routine period of ethical review (especially where the emergency may have disrupted the bodies able to conduct review), and sufficient certainty with respect to the evidence of likely harm and benefit to proceed.

- The health threat **may extend beyond national borders and is a matter of regional and international concern**, in terms of the potential for direct impact on other countries and / or in requiring an international element in the response.

- There are **barriers hindering effective response**. This may be because of scientific uncertainty or other forms of lack of knowledge that prevent a prompt and effective response, regardless of questions of resource. It may also be because of a lack of resources: for example, in terms of finance, personnel, or infrastructure.

Characterised in this way, it is clear that global health emergencies often occur in contexts where certain types of research / research questions are of great value (in order to contribute to more effective response now and / or in the future) and yet also constitute **'radically non-ideal' circumstances** for research to be conducted.[25]

Such contexts may also be 'radically non-ideal' for research in a number of other respects:

- They may pose threats to autonomy, where the need to take action to protect the health of the population as a whole is so great that it may, exceptionally, outweigh respect for individual choices and / or privacy – for example with respect to the use of identifiable data for population-level research, without explicit consent.
- They are likely to be associated with panic, fear, distress, and anxiety, alongside the disruption of community structures and family life.

We reiterate that this suggested working definition deliberately focuses on features of emergencies that might challenge 'standard' approaches to research ethics and research governance. It therefore excludes many important health challenges: for example non-communicable diseases which are not linked with urgency arising out of disruption. This is not a judgment about relative importance either to public or individual health – but rather an acknowledgment that the research challenges generated by these major public health threats appear to be different in kind. It is not, for example, obvious why the very serious and foreseeable threats to global health posed by general antimicrobial resistance or by the growth

[25] Note the paradox that it could also be said to be a radically ideal place for research i.e., there are few other contexts in which research could be said to be as important or valuable: see for example the characterisation of epidemics as providing a "window of opportunity" in some cases to prove the efficacy of vaccines: WHO (2015) *Second WHO high-level meeting on Ebola vaccines access and financing: summary report*, available at: http://apps.who.int/iris/bitstream/handle/10665/149045/WHO_EVD_Meet_HIS_15.1_eng.pdf;jsessionid=E6829DDA23136059BF84CD64CBC893E3?sequence=1, at page 4.

in non-communicable diseases might require us to rethink what constitutes an ethical approach to research, although evidence about the scale of these threats could, and should, affect decisions about funding and prioritisation of such research.[26] On the other hand, a specific outbreak of a drug-resistant variant of a well-known disease – or the traumatic effects on mental health of population displacement during a particular conflict – could constitute a 'disruptive' emergency that challenges assumptions about ethical research in the same way as the outbreak of the Zika virus in Latin America with its previously unknown serious impacts on the fetus.

It has also been argued that many of the features used to justify exceptional action in the West Africa Ebola outbreak could equally well apply in a much wider range of circumstances: not only in more limited or less lethal outbreaks, but also, for example, in the case of people with cancer for whom no therapy exists and who wish to access unproven interventions.[27] This highlights the question of who may have the authority to determine that a particular set of circumstances does, or does not, meet these criteria. (See also **section 5**.)

Back to questions 1 and 2

[26] Note, for example, how the WHO declared the 'end' of the Zika PHEIC in November 2016 on the basis not that the outbreak had ended but that it had become endemic, and hence non-emergency resources needed to be mobilised in a sustainable manner to reduce transmission and disease burden: Jamrozik E, and Selgelid MJ (2018) Ethics, health policy, and Zika: from emergency to global epidemic? *Journal of Medical Ethics* **44(5)**: 343-8.

[27] Calain P (2018) The Ebola clinical trials: a precedent for research ethics in disasters *Journal of Medical Ethics* **44(1)**: 3-8.

Read more: undertaking research in a global health emergency: whose voices should be heard?

There is an inherent tension between, on the one hand, the importance of strong in-country health leadership,[28] and on the other, the international and multi-agency nature of much emergency response. Indeed, a major focus of 'peacetime' planning between emergencies has been on international efforts to identify major threats in order to ensure rapid mobilisation of relevant research whenever and wherever needed. Examples include the recent work by WHO in identifying 'priority pathogens' likely to trigger major infectious disease outbreaks,[29] and the establishment of the WHO Thematic Platform for Health-EDRM (health-related emergency and disaster risk management) to promote the need for greater collaboration and a strategic research agenda in a broader range of emergencies and disasters.[30]

At the same time, alongside such 'centralised' initiatives, there is an increasing focus on building up capacity across regions – particularly with respect to infectious diseases – in order to embed such international initiatives within national and regional systems, promote collaboration, and develop local capacity. Examples include the development of major clinical research networks in English and French-speaking Africa, Latin America, Europe, Australia, and worldwide, supported through the European and Developing Countries Clinical Trial Partnership (EDCTP),[31] and the Global Research Collaboration for Infectious Disease Preparedness (GLOPID-R).[32] Online platforms have similarly been established to share social science and anthropological research that supports the development of locally-appropriate interventions in emergencies.[33] Factors associated with the success of global health research collaborations have been found to include: respect for the needs, interests and agendas of all partners in the collaboration; trust and confidence; and justice and fairness in collaboration.[34] (See also **section 7**.)

Distinct from scientific and professional collaboration, community engagement with populations from which study participants are to be drawn is widely accepted as a crucial component of ethical research, and a necessary element for that research to be successfully

---

28 Nuffield Council on Bioethics (2002) *The ethics of research related to healthcare in developing countries*, available at: http://nuffieldbioethics.org/project/research-developing-countries.

29 WHO (2016) *An R&D blueprint for action to prevent epidemics: plan of action*, available at: http://www.who.int/blueprint/about/r_d_blueprint_plan_of_action.pdf; and WHO (2018) *List of blueprint priority diseases*, available at: http://www.who.int/blueprint/priority-diseases/en/.

30 See, for example, Lo STT, Chan EYY, Chan GKW *et al.* (2017) Health emergency and disaster risk management (Health-EDRM): developing the research field within the Sendai Framework paradigm *International Journal of Disaster Risk Science* **8(2)**: 145-9; and Chan EYY, and Murray V (2017) What are the health research needs for the Sendai Framework? *The Lancet* **390(10106)**: e35-e6.

31 See: EDCTP (15 March 2018) *EDCTP contribution to epidemic preparedness: consortia ALERRT and PANDORA-ID-NET*, available at: https://www.edctp.org/news/edctp-contribution-epidemic-preparedness-consortia-alerrt-pandora-id-net/, announcing the launch of ALERRT in sub-Saharan Africa and PANDORA across all geographical regions of Africa.

32 See: GloPID-R (2017) *Clinical trial networks*, available at: https://www.glopid-r.org/clinical-trial-networks/. These include: REACTing in France, French-speaking Africa and the French Caribbean; REDe – Research Capacity Network which links Zika study sites in Latin America and the Caribbean; PREPARE in Europe; APPRISE in Australia; and ISARIC, a global federation of 55 research networks spanning 11 countries.

33 See, for example, the Ebola Response Anthropology Platform (ERAP) (2108) *Homepage*, available at: http://www.ebola-anthropology.net/; and the Social Science in Humanitarian Action Platform: http://www.socialscienceinaction.org/.

34 Parker M, and Kingori P (2016) Good and bad research collaborations: researchers' views on science and ethics in global health research *PloS One* **11(10)**: e0163579.

completed.[35] At best, 'engagement' should not be about communicating plans agreed elsewhere, but about genuine shared ownership of priorities and research aims.[36]

In practice, the realities of the emergency situation can make shared ownership exceedingly difficult: local communities may be overwhelmed and / or suspicious with respect to the motives of international responders or researchers; there may be inadequate health infrastructure; in many cases there will be competing and conflicting populations or subgroups within the 'community'; there may be a lack of trust between national governments and immediately affected populations,[37] strained political relations, or even a complete lack of legitimate authority in the relevant region, leading to security risks for both local populations and researchers.[38] Depending on the nature of the threat, local scientists may not have had the opportunity to develop the highly specialised expertise required for certain kinds of research, thus adding to the risks of inequitable collaborations.[39] On the other hand, it could be argued that part of the problem is precisely that a focus on high-tech solutions skews the agenda, and may lead to lower-tech approaches (for example focusing on prevention and consistent basic care) not being given fair consideration.[40]

See also section 7 on collaboration.

Back to questions 3–5

[35] See, for example, Gericke CA (2015) Ebola and ethics: autopsy of a failure *BMJ* **350**: h2105; Kummervold PE, Schulz WS, Smout E *et al.* (2017) Controversial Ebola vaccine trials in Ghana: a thematic analysis of critiques and rebuttals in digital news *BMC Public Health* **17(1)**: 642; and EBOVAC Projects (2017) *Training resource: ethical challenges (section 2)*, available at: http://www.ebovac.org/ebodac/training-resource/.

[36] See, for example, Haire BG, and Kaldor JM (2018) Communities need to be equal partners in determining whether research is acceptable *Journal of Medical Ethics* **44(3)**: 159-60 who argue that "The test of an empowered community collaboration is whether the community's voice is respected when it says no".

[37] See, for example, USAID (15 March 2018) *Post-Ebola Guinea builds trust in health system*, available at: https://www.usaid.gov/results-data/success-stories/new-strategy-builds-trust-guinea%E2%80%99s-post-ebola-health-systems on the development of communication strategies in Guinea aiming to build such trust.

[38] See, for example, Anthrologica (2018) Socio-cultural considerations for vaccine introduction and community engagement, available at: https://opendocs.ids.ac.uk/opendocs/ds2/stream/?#/documents/3641122/page/1. See also: Sheehan M (2018) Moral narcissism and moral complicity in global health and humanitarian aid *Journal of Medical Ethics* **44(5)**: 287.

[39] Beran D, Byass P, Gbakima A *et al.* (2017) Research capacity building - obligations for global health partners *The Lancet Global Health* **5(6)**: e567-e8.

[40] See, for example, the discussion in Boozary AS, Farmer PE, and Jha AK (2014) The Ebola outbreak, fragile health systems, and quality as a cure *JAMA* **312(18)**: 1859-60.

Read more: study design and review

Factors influencing ethical and acceptable study design

The question of what constitutes an ethical trial design in an emergency, and whether unproven interventions should be offered outside the context of a clinical trial, has been hotly contested in recent emergencies, and continues to divide opinion. An account of the decisions made by the WHO's own ethics review committee (WHO-ERC) in the 2014-16 outbreak of Ebola in West Africa, for example, notes how the design of interventional trials was "controversial and divided opinions between researchers, physicians, ethicists and regulators". In particular, advocates of RCTs argued for the need for studies to include randomisation to a comparator arm to ensure scientific robustness and social value; while others argued it was unethical to withhold the hope offered by investigational interventions given the unacceptably high fatality rate in West Africa under standard care.[41]

Guidance issued during the outbreak by the WHO's Ethics Working Group emphasised the ethical imperative of carrying out research on potential therapeutic agents, and stated that "all scientifically recognized methodologies and study designs should be considered as ethically acceptable", whether or not they involved randomisation to control groups.[42] However, it noted that some trial designs might not be acceptable to the study population, or feasible for logistical reasons, and suggested that, in this context, designs involving elements of cluster randomisation,[43] stepped wedge,[44] single arm comparison,[45] and adaptive methods[46] might be considered preferable. Further – more detailed – guidance, issued by WHO in 2016, reinforced the importance of methodological rigour in research, noting that "exposing research participants to risk is ethically unacceptable if the study is not designed in a manner capable of providing valid results."[47] Nor will a scientifically 'perfect' study design for which researchers are unable to recruit sufficient participants yield helpful data.

The Ebola trials reviewed (and approved) by the WHO-ERC in 2014-16 included: a single-arm study using historical controls; a comparative non-randomised study with a concurrent control group who received standard care when the supply of the investigational intervention was insufficient; and, for a phase III vaccine trial, a 'ring' design, in which the contacts of patients newly diagnosed with Ebola were randomised either to immediate vaccination or delayed

---

41 Alirol E, Kuesel AC, Guraiib MM *et al.* (2017) Ethics review of studies during public health emergencies - the experience of the WHO ethics review committee during the Ebola virus disease epidemic *BMC Medical Ethics* **18(1)**: 43. See also the account in chapter 2 of National Academies of Sciences, Engineering, and Medicine (2017) *Integrating clinical research into epidemic response: the Ebola experience*, available at: http://nationalacademies.org/hmd/reports/2017/integrating-clinical-research-into-epidemic-response-the-ebola-experience.aspx.

42 WHO (2014) Ethical issues related to study design for trials on therapeutics for Ebola Virus Disease: WHO Ethics Group discussion - summary of discussion, available at: http://apps.who.int/iris/bitstream/handle/10665/137509/WHO_HIS_KER_GHE_14.2_eng.pdf?sequence=1le/10665/137509/WHO_HIS_KER_GHE_14.2_eng.pdf?sequence=1.

43 London School of Hygiene and Tropical Medicine (2018) *Cluster randomised trials*, available at: http://evaluation.lshtm.ac.uk/cluster-randomised-trials/.

44 Hemming K, Haines TP, Chilton PJ *et al.* (2015) The stepped wedge cluster randomised trial: rationale, design, analysis, and reporting *BMJ* **350**.

45 Evans SR (2010) Clinical trial structures *Journal of Experimental Stroke & Translational Medicine* **3(1)**: 8-18, at 2.1.

46 Trials where the design may constantly be modified in response to emerging data – for example reducing the numbers allocated to less promising arms, or closing down/introducing new arms. See, for example, Thorlund K, Haggstrom J, Park JJ *et al.* (2018) Key design considerations for adaptive clinical trials: a primer for clinicians *BMJ* **360**.

47 WHO (2016) *Guidance for managing ethical issues in infectious disease outbreaks*, available at: http://apps.who.int/iris/bitstream/10665/250580/1/9789241549837-eng.pdf, at page 33.

vaccination 21 days later.[48] An expert panel convened by WHO in 2014 also approved "monitored emergency use of unregistered and experimental interventions" (MEURI): that is, use of unproven interventions outside the framework of a trial, providing clinical data were systematically collected and shared.[49] Two such proposals were subsequently approved by the WHO-ERC for use in Sierra Leone and Guinea;[50] and in the latest Ebola outbreak in the Democratic Republic of the Congo in May 2018, 'compassionate use' of an interventional vaccine was similarly approved.[51]

In a subsequent review of the clinical trials conducted during the 2014-16 outbreak, the US National Academies of Science, Engineering and Medicine (NAS) expressed concern that, despite all the resources, time, and effort put in, none of the therapeutic trials was able to reach a definitive conclusion about efficacy.[52] NAS concluded that the RCT *was* an ethical and appropriate design to use, even in such challenging circumstances, while noting that randomisation could take many forms, including individual randomisation, cluster randomisation, and adaptive designs. Considerable concern was expressed about the use of unproven interventions outside a trial, with the conclusion that such use "not only fails to provide information on safety or efficacy, but also creates inequities with the larger affected population during an epidemic. Such uses can promote the public misconception that a safe and effective treatment exists and may generate mistrust of researchers and research efforts that will make it more difficult to launch clinical trials when additional interventions become available".[53]

'Alternative' clinical trial designs were further debated at the 2017 Global Forum on Bioethics in Research, an annual event that seeks to bring the voices and perspectives of low- and middle-income countries to the fore in discussions on emerging ethical issues in research.[54] It was widely agreed that it was more helpful to consider, in any specific context, what was the best design for the goals of a study, rather than thinking in terms of 'standard' and 'alternative' designs. However, while approaches including adaptive, cluster randomised, and stepped wedge designs were agreed to offer a number of potential advantages, it was noted that they also raised novel ethical questions. These included:

---

48 Alirol E, Kuesel AC, Guraiib MM *et al.* (2017) Ethics review of studies during public health emergencies - the experience of the WHO ethics review committee during the Ebola virus disease epidemic *BMC Medical Ethics* **18(1)**: 43.

49 WHO (2014) *Ethical considerations for use of unregistered interventions for Ebola viral disease: report of an advisory panel to WHO*, available at: http://apps.who.int/iris/bitstream/handle/10665/130997/WHO_HIS_KER_GHE_14.1_eng.pdf?sequence=1. Further guidance on use of MEURI was subsequently issued in WHO (2016) *Guidance for managing ethical issues in infectious disease outbreaks*, available at: http://apps.who.int/iris/bitstream/10665/250580/1/9789241549837-eng.pdf.

50 Alirol E, Kuesel AC, Guraiib MM *et al.* (2017) Ethics review of studies during public health emergencies - the experience of the WHO ethics review committee during the Ebola virus disease epidemic *BMC Medical Ethics* **18(1)**: 43.

51 WHO (23 May 2018) Frequently asked questions on compassionate use of investigational vaccine for the Ebola virus disease outbreak in Democratic Republic of the Congo, available at: http://www.who.int/ebola/drc-2018/faq-vaccine/en/.

52 National Academies of Sciences, Engineering, and Medicine (2017) *Integrating clinical research into epidemic response: the Ebola experience*, available at: http://nationalacademies.org/hmd/reports/2017/integrating-clinical-research-into-epidemic-response-the-ebola-experience.aspx.

53 Ibid., at page 43.

54 Global Forum on Bioethics in Research (2017) *Ethics of alternative clinical trial designs and methods in low- and middle-income country research: 28-29 November, Bangkok*, available at: https://www.wellcomeevents.org/WELLCOME/media/uploaded/EVWELLCOME/event_535/GFBR_Bangkok_summary_slides.pdf. See also the case studies debated at the forum for an account of these different trial designs in a range of settings, pp10ff.

- in **cluster trials**, defining who is the participant, and the implications for consent, particularly where the focus of the research is on different ways of delivering services between 'clusters' based on clinics or geographical communities;
- in **stepped wedge trials**, distinguishing between research and implementation studies, and dealing with local pressures to decide on the sequence of clusters receiving the intervention; and
- for **adaptive trials**, the challenges of achieving informed consent for particularly complex study designs.

It was further noted that there was very limited ethical guidance currently available on these designs, and that research ethics committees in some countries were hesitant to accept them at present because lack of familiarity contributed to concerns as to their ethical acceptability.

Broader ethical questions about study design, and indeed study prioritisation, arise in connection with the question of how contemporary needs should be prioritised over those of potential beneficiaries in the future: for example through the use of broad inclusion criteria and accommodation of compassionate use.[55] An issue of particular concern during the 2014-2016 Ebola outbreak was the automatic exclusion of pregnant women, for example at the behest of the insurers of the companies developing novel interventions, despite very high fatality rates.[56] This issue has since been extensively debated, and the importance of access by pregnant women reiterated,[57] although at the time of writing this group has still been excluded from access to the compassionate use of an investigational vaccine being made available in the latest Ebola outbreak in the DRC.[58] MSF has, in the past, taken the clear stance that studies involving participants accessed via MSF treatment centres should have the potential to benefit those affected at the time, and should not exclude any groups who might potentially benefit. Logistical factors such as whether research interventions are available now in sufficient quantity, and can be sustainably administered in this particular setting, may thus affect consideration of what studies are judged ethically acceptable.[59] Similarly, negotiations with suppliers over the affordability of interventions may lead to significant delays in establishing clinical trials, thereby affecting both their viability, and the possibility of affected populations receiving direct benefit.[60]

---

55 See, for example, Eyal N, and Lipsitch M (2017) Vaccine testing for emerging infections: the case for individual randomisation *Journal of Medical Ethics*: Published online first: 10 April 2017; Folayan MO, Haire B, Allman D *et al.* (2018) Research priorities during infectious disease emergencies in West Africa *BMC Research Notes* **11(1)**: 159.

56 Gomes MF, de la Fuente-Núñez V, Saxena A *et al.* (2017) Protected to death: systematic exclusion of pregnant women from Ebola virus disease trials *Reproductive Health* **14(supplement 3)**: 172.

57 See, for example Proceedings from the Global Forum on Bioethics in Research (GFBR)'s 'Ethics of research in pregnancy' meeting (2016), available at: https://reproductive-health-journal.biomedcentral.com/articles/supplements/volume-14-supplement-3; and Ethics Working Group on ZIKV Research and Pregnancy (2017) *Pregnant women and the Zika virus vaccine: research agenda*, available at: http://guidance.zikapregnancyethics.org/wp-content/uploads/2017/08/Full+Guidance-Pregnant-Women-the-Zika-Virus-Vaccine-Research-Agenda_optimized.pdf.

58 WHO (23 May 2018) Frequently asked questions on compassionate use of investigational vaccine for the Ebola virus disease outbreak in Democratic Republic of the Congo, available at: http://www.who.int/ebola/drc-2018/faq-vaccine/en/.

59 Rid A, and Antierens A (2017) How did Médecins Sans Frontières negotiate clinical trials of unproven treatments during the 2014–2015 Ebola epidemic?, in *The politics of fear*, Hofman M, and Au S (Editors) (Oxford: Oxford University Press).

60 Personal experience within the working group; see also Lang T (2015) Ebola: embed research in outbreak response *Nature* **524(7563)**.

Process of ethical review

While the West Africa Ebola outbreak put exceptional pressure on research ethics committees to review multiple studies in short timeframes, it also demonstrated the scope for ethical review to be flexible and supportive of researchers' needs in emergencies. The WHO-ERC, for example, established a subcommittee to focus specifically on Ebola studies, and was able to offer accelerated review within an average of six working days.[61] Qualitative research with members of ethics committees engaged with humanitarian research similarly identified "timeliness, responsiveness and rigorousness" as key elements in effective review of studies in a wide range of disasters.[62]

Questions of capacity, however, remain a challenge for research ethics committees in many countries.[63] Some committees in countries affected by recent Ebola outbreaks have struggled to deal with the sudden large increase in the number of protocols presented to them, and would have valued some kind of prioritisation process, especially where multiple and uncoordinated studies were forwarded from the ethics committees of institutions from high income countries.[64] These questions of capacity, and the associated need for support, are even more likely to arise in the context of the many global health emergencies that fail to attract the degree of public attention devoted to the 2014-16 Ebola outbreak. However, proposed approaches such as the use of joint committees for a single multi-country ethical review process have received a sceptical response because of the risk that local ownership in countries hosting the research may be lost.[65] It is also essential that local processes of review are seen to be independent, as well as robust, in order to maintain trust among potential participants.[66] Further difficulties arise in circumstances, such as in emergencies linked with internal conflict, where there may simply be nobody available with local legitimacy to undertake ethical scrutiny.

As noted above, where novel designs, with which ethics committees are not familiar and which are not well covered by existing guidance, are presented for approval in an emergency, this creates additional challenges for research ethics committees. The idea of 'pre-approval' or 'pre-review' of generic protocols, or of particular aspects of protocols, has been mooted as one possible way of enabling studies to go ahead speedily in emergencies, especially where less familiar designs are involved.[67] However, while such early sight of possible study designs

---

61 Alirol E, Kuesel AC, Guraiib MM *et al.* (2017) Ethics review of studies during public health emergencies - the experience of the WHO ethics review committee during the Ebola virus disease epidemic *BMC Medical Ethics* **18(1)**: 43.

62 Hunt M, Tansey CM, Anderson J *et al.* (2016) The challenge of timely, responsive and rigorous ethics review of disaster research: views of research ethics committee members *PloS One* **11(6)**: e0157142.

63 See, for example, OSIWA, WATER, and IRESSEF (2017) Training meetings for ethics committee members in West Africa on emerging and re-emerging infectious disease epidemics: Diamniadio, 25-27 September, available at: http://nhvmas-ng.org/site/wp-content/uploads/2018/03/Report-WATER-Bioethics-training-meeting.pdf.

64 Personal communication from Patricia Kingori; see also: Schopper D, Ravinetto R, Schwartz L *et al.* (2017) Research ethics governance in times of Ebola *Public Health Ethics* **10(1)**: 49-61.

65 ALERRT (2018) *"Ethics preparedness": facilitating ethics review during outbreaks - recommendations arising from a joint ALERRT & WHO workshop*, available at: https://www.alerrt.global/sites/www.alerrt.org/files/2018-06/alerrt_workshop_recommendations_final_30may18_0.pdf.

66 See, for example, Tangwa G (2017) Ebola vaccine trials, in *Ethics dumping: case studies from North-South research collaborations*, Schroeder D, Cook J, Hirsch F, Fenet S, and Muthuswamy V (Editors) (Cham, Switzerland: Springer Open).

67 Hunt M, Tansey CM, Anderson J *et al.* (2016) The challenge of timely, responsive and rigorous ethics review of disaster research: views of research ethics committee members *PloS One* **11(6)**: e0157142.

could play a positive role in enabling committees to familiarise themselves with novel methodologies and their ethical implications, close scrutiny of final proposals will still be required before ethical approval can be granted.[68]

Features of a 'global health emergency' described in the first section of this paper – such as the disruptive and dangerous nature of the situation, and associated fear and panic – may also make the role of ethical review more challenging for committee members, and encourage them to take a more restrictive approach than might otherwise be the case. In a workshop hosted in 2016 by the Nuffield Council, it was suggested that one way of conceptualising a proportionate approach to review in these circumstances was consideration of 'errors that matter':[69] focusing, for example, on the potential for the research to cause physical harm to participants or increase psychological stress; loss of community trust; or risks to the quality of data that could undermine or negate the value of the research.[70]

Back to questions 6–10

[68] ALERRT (2018) *"Ethics preparedness": facilitating ethics review during outbreaks - recommendations arising from a joint ALERRT & WHO workshop*, available at: https://www.alerrt.global/sites/www.alerrt.org/files/2018-06/alerrt_workshop_recommendations_final_30may18_0.pdf.

[69] See: Clinical Trials Transformation Initiative (2015) *CTTI recommendations: quality by design*, available at: https://tracs.unc.edu/docs/regulatory/CTTI_Recommendations-Quality_by_Design.pdf.

[70] Nuffield Council on Bioethics (2016) *Research and innovation in global health emergencies: ethical challenges*, available at: http://nuffieldbioethics.org/wp-content/uploads/Global-health-emergencies-short-note.pdf.

Read more: making decisions about participation in research

The challenges of seeking sufficiently informed consent for research participation even in non-emergency settings are well documented. Even without the pressure of time, it can be difficult to explain essential elements of a complex study in ways that are meaningful to those unfamiliar with medical research; and judgments about a person's capacity, and about their freedom to act voluntarily can be very finely balanced. In contrast, in the case of non-interventional studies that pose very low burdens on participants, such as those concerned with improving health systems, detailed and complicated consent processes may deter potential participants who would otherwise have been willing to take part.

In both high- and low-income settings, participation in medical research may be desirable as a way of obtaining interventions that are unavailable through standard health services.[71] Where people have poor, or no, access to even basic health services, the ancillary care involved in much medical research is a sufficient benefit itself to motivate people to participate, regardless of other factors.[72] Particular dilemmas arise for researchers where local decision-making practices – for example exclusion of women – are incompatible with international norms.[73]

Much has also been written about the risks of 'therapeutic misconception', where research participants wrongly assume that research interventions, such as additional blood draws or data collection, are designed to improve their care, rather than for longer-term purposes of improving the evidence base for the care of others in the future.[74]

In a global health emergency, any and all of these challenges to voluntary and informed decision-making may be exacerbated by factors such as disruption, fear and panic, family separation, and lack of access to basic resources and services. Additional dilemmas associated with emergencies, particularly those involving novel pathogens or other health threats for which no effective treatments are currently available, include:

- **Dealing with uncertainty**: the uncertainty inherent in any research study is likely to be exacerbated in an emergency, where in some cases it may be less risky to proceed on the basis of imperfect information, rather than wait, for example for confirmatory findings (see **section 3**). There is, therefore, a degree to which consent to participation in research in such circumstances is unavoidably 'broad' rather than specific: that is, a decision to give consent is a decision to authorise others to act, despite the uncertainty. This highlights the central role played by trust, and trustworthiness, in such circumstances, alongside the role of more formal protections offered through the process of ethical review.

- **Heightened risks of participation / non-participation**. The risks involved in novel interventions, particularly where these are offered in a research study where no effective treatments currently exist, may be higher than usual both for those who

---

71 See, for example, BBC News Online (25 May 2018) *Cancer patient feels 'privileged to be alive' after NHS trial treatment*, available at: http://www.bbc.co.uk/news/health-44238136.

72 Mfutso-Bengo J, Manda-Taylor L, and Masiye F (2014) Motivational factors for participation in biomedical research: evidence from a qualitative study of biomedical research participation in Blantyre District, Malawi *Journal of Empirical Research on Human Research Ethics* **10(1)**: 59-64; Kingori P (2015) The 'empty choice': a sociological examination of choosing medical research participation in resource-limited Sub-Saharan Africa *Current Sociology* **63(5)**: 763-78.

73 Nuffield Council on Bioethics (2002) *The ethics of research related to healthcare in developing countries*, available at: http://nuffieldbioethics.org/project/research-developing-countries.

74 Henderson GE, Churchill LR, Davis AM *et al.* (2007) Clinical trials and medical care: defining the therapeutic misconception *PLoS Medicine* **4(11)**: e324.

participate, and for those who decline or are ineligible to participate (in the sense of lost opportunity to benefit should results be beneficial). These heightened risks add to the challenges of decision-making, particularly where potential participants are in potentially vulnerable situations. This might include children, especially where they are not supported by those in a parental role; and those with limited or impaired capacity.

Back to questions 11–13

Read more: duties at the interface of research, treatment and public health

Research and treatment

Traditionally, ethical guidance has distinguished sharply between 'research' (understood as the endeavour to generate knowledge for future benefit) and 'treatment' (concerned with individual benefit now).[75] However, research interventions may at the same time have a therapeutic effect: for example where novel treatments provided in the context of research prove more effective than existing alternatives. In circumstances where there is a sense of great urgency, and there are no existing effective treatments, it is important to recognise that participants will give consent in order to access what they hope may be the best available treatment.[76] Despite concerns about 'therapeutic misconception' (where research-related procedures are misunderstood as having a therapeutic aim), in some cases, decisions to participate in research may be based on accurate perceptions of benefit, for example through access to ancillary care.[77] Even without ancillary care benefits, such a decision may still be a rational choice, on the basis that participation may appear to offer the only source of hope, however uncertain – for example where there is no evidence of any kind of benefit from 'standard' care. This role of hope (described by one author as an "important community value"[78]) also highlights the responsibilities of those who offer such hope.

Even where research participation may offer some prospect of direct benefit, however, it will also involve extra procedures (such as research-related blood draws, and data collection), in addition to the novel intervention itself. In other cases, the research will involve such features without the possible benefit of a novel intervention. There is thus an inherent tension for front-line care staff of responding to a situation where there are very high levels of suffering, and of also taking time to conduct research. This is an issue both for the staff themselves in how they prioritise their time; and at the level of funding decisions, including how the funding available is prioritised between care and research.

Research and public health

Just as 'research' and 'treatment' are treated as separate domains of practice, 'research' and 'public health' practice are also commonly conceptualised as distinct activities. Guidance by WHO on public health surveillance, for example, states that individual informed consent for the collection of such data is not always required: for example where this would be prohibitively costly, unfeasible, or unwarranted because the risks are low.[79] Such data may, however, at

---

[75] Faden RR, Kass NE, Goodman SN *et al.* (2013) An ethics framework for a learning health care system: a departure from traditional research ethics and clinical ethics *Hastings Center Report* **43(s1)**: S16-S27.

[76] See, for example, Folayan MO, Haire B, Allman D *et al.* (2018) Research priorities during infectious disease emergencies in West Africa *BMC Research Notes* **11(1)**: 159.

[77] See, for example, Mfutso-Bengo J, Ndebele P, Jumbe V *et al.* (2008) Why do individuals agree to enrol in clinical trials? A qualitative study of health research participation in Blantyre, Malawi *Malawi Medical Journal: The Journal of Medical Association of Malawi* **20(2)**: 37-41; Mwangi R, Ndebele P, and Mongoven A (2017) Understanding, therapeutic misconceptions and perceptions, and enrollment decision-making: a pediatric preventive malaria trial in rural Tanzania *IRB: Ethics & Human Research* **39(5)**; Tengbeh AF, Enria L, Smout E *et al.* (2018) "We are the heroes because we are ready to die for this country": participants' decision-making and grounded ethics in an Ebola vaccine clinical trial *Social Science & Medicine* **203**: 35-42.

[78] Folayan MO, Haire B, Allman D *et al.* (2018) Research priorities during infectious disease emergencies in West Africa *BMC Research Notes* **11(1)**: 159.

[79] WHO (2017) *WHO guidelines on ethical issues in public health surveillance*, available at: http://apps.who.int/iris/bitstream/handle/10665/255721/9789241512657-eng.pdf;jsessionid=25196958F641A3B2FBE863AEB1968122?sequence=1, at page 40. See also:

times need to be identifiable to meet particular public health needs: for example to avoid double-counting in surveillance, and to enable contact tracing in responding to infectious disease.[80] The collection of the same (identifiable) data for purposes described as 'research', would, in contrast, be subject to ethical review processes and require individual consent.[81] Such different approaches are likely to hinder data-sharing in emergencies, despite the clear guidance issued by the WHO in 2016 that "all individuals and entities involved in [data generating] activities should cooperate by sharing relevant and accurate data in a timely manner".[82]

Even outside the emergency context, it has been argued that population-based research has, in fact, far more in common with public health practice than with 'medical' research, and that the "ethical challenges presented in population-based research need to be considered within a less individualist ethical framework because requirements such as informed consent and privacy, which have an important place in medical research ethics, may not be sufficient or appropriate to provide guidance."[83] Such a shift, however, would require some serious re-thinking of whether the current demarcations between public health practice and research are sustainable.

Research and evaluation / audit

A further grey area emerges between research (particularly health systems research) and activities designed to evaluate or audit current practice. It was argued at the 2017 Global Forum on Bioethics in Research that in such cases it was less helpful to focus on a correct 'classification', and more helpful instead to consider the nature of the ethical concerns raised in the particular circumstances, and what oversight would be most appropriate to identify and respond to them.[84]

Competing ethical norms within humanitarian response

Front-line staff working within these fields of research, medical care, wider humanitarian assistance, and public health, often operate with different regulatory and ethical norms and practices.[85] These differences may emerge between different healthcare professions, for example between psychologists and surgeons, or across different health sectors such as global health academics and staff working for non-governmental organisations. Those providing direct healthcare and humanitarian assistance to people affected by global health

---

Nuffield Council (2007) *Public health: ethical issues*, available at: http://nuffieldbioethics.org/project/public-health, at page xxi.

80 WHO (2017) *WHO guidelines on ethical issues in public health surveillance*, available at: http://apps.who.int/iris/bitstream/handle/10665/255721/9789241512657-eng.pdf;jsessionid=25196958F641A3B2FBE863AEB1968122?sequence=1, at page 38.

81 CIOMS (2016) *International ethical guidelines for health-related research involving humans*, available at: https://cioms.ch/wp-content/uploads/2017/01/WEB-CIOMS-EthicalGuidelines.pdf, guideline 12.

82 WHO (2016) *Guidance for managing ethical issues in infectious disease outbreaks*, available at: http://apps.who.int/iris/bitstream/10665/250580/1/9789241549837-eng.pdf, at page 38.

83 Lignou S (2018) Informed consent in cluster randomised trials: new and common ethical challenges *Journal of Medical Ethics* **44(2)**: 114-20. See also: Ballantyne A, and Schaefer GO (2018) Consent and the ethical duty to participate in health data research *Journal of Medical Ethics* **44(6)**: 392.

84 Global Forum on Bioethics in Research (2017) *Ethics of alternative clinical trial designs and methods in low- and middle-income country research: 28-29 November, Bangkok*, available at: https://www.wellcomeevents.org/WELLCOME/media/uploaded/EVWELLCOME/event_535/GFBR_Bangkok_summary_slides.pdf.

85 See, for example, WHO (2015) *Ethics in epidemics, emergencies and disasters: research, surveillance and patient care - training manual*, available at: http://apps.who.int/iris/bitstream/handle/10665/196326/9789241549349_eng.pdf?sequence=1.

emergencies are often well placed to conduct research but will not necessarily be familiar with the requirements of research ethics guidance and processes, and may be overwhelmed responding to direct care needs.[86] Research is often regarded as secondary to activities concerned with public health and care for individuals. However, it has been argued that there is an ethical imperative to collect information systematically in order to improve emergency response in the future, and that a failure to do so fails future generations of those exposed to inadequate practice.[87]

Back to questions 14–17

[86] See, for example, Richardson T, Johnston AM, and Draper H (2017) A systematic review of Ebola treatment trials to assess the extent to which they adhere to ethical guidelines *PloS One* **12(1)**: e0168975, which noted how in one case clinicians felt that treating 100 patients consecutively for compassionate reasons did not constitute a clinical trial.

[87] Blanchet K, Ramesh A, Frison S *et al.* (2017) Evidence on public health interventions in humanitarian crises *The Lancet* **390(10109)**: 2287-96, at 2293.

Read more: obligations to, and expectations of, front-line research staff

WHO guidance, issued in 2016 on managing ethical issues in infectious disease outbreaks, provides detailed advice on the rights and obligations of front-line response workers, which could be applied by analogy also to front-line research workers.[88] Given the risks that front-line workers may run in order to meet the expectations placed upon them, it is suggested that governments and others owe them reciprocal obligations to:

- minimise the risk of possible infection, through the provision of appropriate training, tools and resources;[89]
- provide access to the 'highest level of care reasonably available' should staff or their immediate family members become ill (including consideration of priority access to vaccines and other treatments as they become available);
- ensure fair remuneration, including financial support during illness associated with their role;
- provide support for reintegration, recognising the risks of stigmatisation and discrimination that may be associated with their role (which governments should also make efforts to reduce); and
- give assistance to family members, where this is necessary because of the nature of the front-line staff member's role.

Where such front-line workers are deployed from abroad, the guidance further emphasises the responsibilities of the foreign governments and humanitarian aid organisations responsible for their deployment. These include: clarity about the terms and conditions of their deployment, including what healthcare will be available if they fall ill; action to ensure their security and safety; and provision of necessary training and resources.[90]

In the context of a wider range of humanitarian crises, including natural and manmade disasters, guidance issued by the UN's Inter-Agency Standing Committee on the conduct of ethical mental health and psychosocial research in such settings similarly emphasises the potential safety risks to researchers, including the presence of armed actors, unpredictable events and engaging with communities that have been displaced.[91] The IASC emphasises the importance of "having safeguards, security measures and exit strategies" as part of ethical research practice; and the associated need for coordinating closely with agencies managing the emergency response, monitoring and responding to changing security contexts.

While the WHO and others clearly spell out responsibilities of both governments and employing organisations to those working on the front-line, in practice, direct lines of accountability may be less than clear, particularly where research activity crosses organisational boundaries and involves complex collaborations (see also **section 7**). Thus, the responsibilities of those with 'hidden power', such as those funding research, and the home

---

88 WHO (2016) *Guidance for managing ethical issues in infectious disease outbreaks*, available at: http://apps.who.int/iris/bitstream/10665/250580/1/9789241549837-eng.pdf, pp43-6.

89 Such support may be regarded as a necessary component of any duty to run personal risks as a healthcare professional in such cases: see, for example, Kpanake L, Tonguino TK, Sorum PC *et al.* (2018) Duty to provide care to Ebola patients: the perspectives of Guinean lay people and healthcare providers *Journal of Medical Ethics*: published first online: 21 May.

90 WHO (2016) *Guidance for managing ethical issues in infectious disease outbreaks*, available at: http://apps.who.int/iris/bitstream/10665/250580/1/9789241549837-eng.pdf, pp47-9.

91 IASC (2014) *Recommendations for conducting ethical mental health and psychosocial research in emergency settings*, available at: https://interagencystandingcommittee.org/system/files/1._iasc_recommendations_for_ethical_mhpss_research_in_emergency_settings_0.pdf, at page 44.

research institutions of expatriate principal investigators, may be less well recognised than those with direct employment and line management relationships with front-line staff. However, in practice the decisions and priorities of such organisations may have a strong bearing on what happens on the ground.

There also remain a number of ethically-challenging issues with respect to the role of front-line workers, on which there is as yet little consensus. These include:

- **How to determine the appropriate level of healthcare**, where this is required. If expatriate staff have access to the best available care (including standards of care that cannot feasibly be provided more widely) on the basis that their work is exposing them to dangers that they would otherwise not face, does this justification also apply to local staff? Wherever distinctions are drawn (for example, between front-line staff and local populations, between expatriate and local workers, or between expatriate staff from different continents) difficult questions of fairness arise.[92]

- **The availability of timely ethics training, support and advice** for those on the front line of research: recognising that ethical challenges are not simply 'dealt with' at the ethical review stage, but may emerge at any point during the study.

Finally, those working on the front-line of research do themselves owe obligations consistent with their role, both to research participants and to the wider community. As noted earlier, WHO advises that these obligations include participating in public health efforts through appropriate data sharing, and promoting responsible communication with local communities. These responsibilities highlight the role of character, virtue and personal conduct, for example in how individuals interpret these responsibilities, and in how they handle difficult situations that may not be clearly envisaged by guidelines or in the ethical review process. These concerns arise in reverse in the context of the risks of abusive behaviour by those on the front line.[93]

Back to questions 18–21

[92] See, for example, the discussion in Draper H, and Jenkins S (2017) Ethical challenges experienced by UK military medical personnel deployed to Sierra Leone (operation GRITROCK) during the 2014-2015 Ebola outbreak: a qualitative study *BMC Medical Ethics* **18(77)**.

[93] See, for example, Arie S (2018) Global medical aid charities and allegations of sexual misconduct and crime *BMJ* **361**; CONCORD (9 May 2018) *Safeguards against sexual exploitation and abuse in development and humanitarian action - European NGOs action points*, available at: https://concordeurope.org/2018/05/09/safeguarding-development-seamus-jeffreson/.

Read more: what are the challenges of effective collaboration in global health emergencies?

Effective research in global health emergencies involves international collaboration between multiple organisations and individuals, including different research groups, health professionals, institutions, funders and regulators, with often conflicting priorities, responsibilities and interests.[94] These 'research-focused' stakeholders also need to interact effectively with those responsible for, or engaged with, other aspects of humanitarian response, including domestic authorities, health services and other local leaders and agencies, international aid organisations of various kinds (intergovernmental, other governmental, charitable), private sector partners, and the military.[95] Crucially they also need to keep in view how the actions of external parties, all coming together at this one point in time, intersect with the trajectory of the lives of those affected: for example how past experiences of the actions of NGOs, or of research, will affect present-day expectations and fears.[96]

As noted earlier (see **section 5**), in some cases research elements of humanitarian response may be fully integrated into healthcare, as in the case of trials of novel treatments or vaccines, or where standing operating procedures enable the collection of data for both clinical and research purposes without duplication.[97] In other cases, the research activities may be distinct, but can only be effectively carried out with the cooperation of those concerned with other aspects of response.[98] Where the military are involved in any aspect of humanitarian response, there may be additional challenges in ensuring appropriate conditions in which to conduct research ethically, especially where concerns about complicity may arise.[99]

Even without taking into account the question of the integration of research actors, the leadership and co-ordination of humanitarian response efforts more broadly has recently been criticised as being "too cumbersome, bureaucratic, inadequate in terms of effect and accountability, too dominated by developed countries and insufficiently adapted to constantly changing environments."[100] In the specific context of research, the number of research groups involved in the 2014-2016 West Africa Ebola outbreak led to what has been criticised as an

---

94 Feldman PH, Nadash P, and Gursen M (2002) Researchers from Mars, policymakers from Venus *Health Affairs* **21(4)**: 299-300. See also: Katz R, Blazes D, Bae J *et al.* (2014) Global health diplomacy training for military medical researchers *Military Medicine* **179(4)**: 364-9.

95 Chatham House (2017) *The next Ebola: considering the role of the military in future epidemic response*, available at: http://www.chathamhouse.org/sites/default/files/events/2017-03-31-next-ebola-role-of-military-meeting-summary.pdf.

96 Pringle J (17 July 2017) *Lessons in research ethics: experiences of clinical research participation during the West Africa Ebola crisis* (Keble College, Oxford: Oxford Global Health and Bioethics International Conference).

97 Rojek AM, Dunning J, Leliogdowicz A *et al.* (2017) Regulatory and operational complexities of conducting a clinical treatment trial during an Ebola virus disease epidemic *Clinical Infectious Diseases*: cix1061-cix.

98 See, for example, National Academies of Sciences, Engineering, and Medicine (2017) *Integrating clinical research into epidemic response: the Ebola experience*, available at: http://nationalacademies.org/hmd/reports/2017/integrating-clinical-research-into-epidemic-response-the-ebola-experience.aspx, at chapter 9. See also: IASC (2014) *Recommendations for conducting ethical mental health and psychosocial research in emergency settings*, available at: https://interagencystandingcommittee.org/system/files/1._iasc_recommendations_for_ethical_mhpss_research_in_emergency_settings_0.pdf.

99 Buth P, de Gryse B, Healy S *et al.* (2018) 'He who helps the guilty, shares the crime'? INGOs, moral narcissism and complicity in wrongdoing *Journal of Medical Ethics* **44(5)**: 299-304.

100 Spiegel PB (2017) The humanitarian system is not just broke, but broken: recommendations for future humanitarian action *The Lancet* (special series).

"unorchestrated land grab" for sites and patients.[101] In practice, humanitarian organisations providing direct healthcare on the ground may be highly influential in determining medical research priorities, and facilitating some studies in preference to others, because they act as gatekeepers to many of the potential participants.[102]

In recognition of these significant practical challenges to effective implementation of research aspects of humanitarian response, a number of important initiatives and networks exist to promote collaboration (see also **section 2**). These include:

- the WHO-led R&D Blueprint – a global strategy and preparedness plan that allows the rapid activation of R&D activities during epidemics, including social science research supporting effective communication and response;[103]
- the Global Outbreak Alert Response Network (GOARN) – a network of collaborating institutions and networks, co-ordinated by WHO, which can quickly deploy relevant personnel (including in a research capacity) in response to requests by host countries;[104]
- the Global Research Collaboration for Infectious Disease Preparedness (GloPID-R) which brings together funding organisations and facilitates effective rapid response, research and innovation;[105]
- the Coalition for Epidemic Preparedness Innovations (CEPI) – an alliance between governments, industry, academia, intergovernmental organisations and philanthropic organisations, with a remit to finance and coordinate the development of new vaccines;[106]
- the Pandemic Influenza Preparedness (PIP) Framework which plays an important role in facilitating sharing of influenza virus samples, and in the development of, and access to, vaccines by low income countries;[107]
- the Infectious Diseases Data Observatory (IDDO) – a data sharing platform that seeks to promote collaboration across the research and humanitarian relief sectors in order to maximise the use of available data and improve the quality of future research in infectious diseases;[108]
- the development of a global code of conduct for research in resource-poor settings by the TRUST – Equitable Research Partnerships project;[109] and
- initiatives by Wellcome to identify and promote good practices in data sharing in low income settings.[110]

---

[101] Lang T (2015) Ebola: embed research in outbreak response *Nature* **524(7563)**.

[102] Rid A, and Antierens A (2017) How did Médecins Sans Frontières negotiate clinical trials of unproven treatments during the 2014–2015 Ebola epidemic?, in *The politics of fear*, Hofman M, and Au S (Editors) (Oxford: Oxford University Press).

[103] WHO (2016) *An R&D blueprint for action to prevent epidemics: plan of action*, available at: http://www.who.int/blueprint/about/r_d_blueprint_plan_of_action.pdf; WHO (2018) *Annual review of the blueprint list of priority diseases*, available at: http://www.who.int/blueprint/en/.

[104] WHO (2018) *Global Outbreak Alert and Response Network (GOARN)*, available at: http://www.who.int/ihr/alert_and_response/outbreak-network/en/.

[105] GloPID-R (2018) *Homepage*, available at: https://www.glopid-r.org/.

[106] CEPI (2018) *Homepage*, available at: http://cepi.net/.

[107] WHO (2018) *Pandemic influenza preparedness (PIP) framework*, available at: http://www.who.int/influenza/pip/en/.

[108] IDDO (2018) *About IDDO*, available at: https://www.iddo.org/about-iddo.

[109] TRUST Equitable Research Partnerships (2018) *Global code of conduct for research in resource-poor settings,* available at www.globalcodeofconduct.org.

[110] Wellcome (2018) *Sharing health research data in low-resource settings: supporting necessary infrastructure and building on good practices*, available at: https://figshare.com/articles/Sharing_health_research_data_in_low-

Important questions relating to the fairness of research collaborations also arise, both at the level of individual researchers and at the level of institutions. The Research Fairness Initiative (RFI) identifies three distinct elements of fairness in international research collaborations: 'fairness of opportunity' before the research happens; 'fair process' during research; and 'fair benefit sharing' after research has been completed.[111] The RFI acknowledges that, while partnerships often begin at a personal level between researchers, it is the policies and procedures that prevail at institutional and national level that may ultimately determine how fairly the opportunities and benefits of research are shared.

Recent polling of the International Advisory Board of *Lancet Global Health* on questions of authorship illustrated some of the challenges that arise in ensuring fair involvement and recognition of researchers in low income countries, given the greater power and resources of their partners.[112] Respondents agreed that it would be unacceptable to publish papers drawing on primary data collected in another country without recognising the co-authorship of collaborators from that country. However, there were much more mixed views about the use of open access datasets, and whether it was acceptable to analyse such secondary data without the involvement, and crediting, of those with the knowledge of the context of which it had been collected. It seems likely that these challenges of ensuring genuinely fair collaborations and avoiding 'parachute' research will be significantly exacerbated during an emergency, with the associated pressures of time and disruption of normal structures.

Finally, procedures for the effective sharing, both of data and of biological samples, have been identified as key challenges in the conduct of research in global health emergencies.[113] The sharing of biological samples is particularly challenging because, unlike data, samples represent a limited resource that is depleted by use, raising important questions of prioritisation of access, alongside ethical concerns as whether consent for its use, and possible transfer out of country, has been sufficiently informed and appropriate governance arrangements are in place.[114]

On data, the 2016 WHO guidance on ethical issues in infectious disease outbreaks highlights how data sharing takes on increased urgency "because of the uncertain and ever-changing scientific information; the compromised response capacity of local health systems; and the heightened role of cross-border collaboration".[115] However, different ethical traditions in research and public health (see also **section 5**) may in practice still hinder or delay such effective sharing of data, especially where researchers are concerned that this may risk breaching confidentiality or the terms of the consent which they have sought for use of the data. Surveillance data held by ministries of health, in particular, could potentially provide a

resource_settings_Supporting_necessary_infrastructure_and_building_on_good_practices/6042047/1.

111 Research Fairness Initiative (2018) *RFI - in practice*, available at: http://rfi.cohred.org/how-does-it-work-in-practice/.

112 The Lancet Global H (2018) Closing the door on parachutes and parasites *The Lancet Global Health* **6(6)**: e593.

113 Wellcome (2018) Data sharing in public health emergencies: a study of current policies, practices and infrastructure supporting the sharing of data to prevent and respond to epidemic and pandemic threats, available at: https://figshare.com/articles/Data_sharing_in_public_health_emergencies_A_study_of_current_policies_practices_and_infrastructure_supporting_the_sharing_of_data_to_prevent_and_respond_to_epidemic_and_pandemic_threats/5897608.

114 WHO (2016) *Guidance for managing ethical issues in infectious disease outbreaks*, available at: http://apps.who.int/iris/bitstream/10665/250580/1/9789241549837-eng.pdf, pp39-40.

115 WHO (2016) *Guidance for managing ethical issues in infectious disease outbreaks*, available at: http://apps.who.int/iris/bitstream/10665/250580/1/9789241549837-eng.pdf, at page 38.

valuable research resource, but many factors, including political considerations, lack of resource to handle requests, and reported past misconduct by international actors, may hinder effective sharing. Concerns about impact on their future publications and academic opportunities may also hold back some researchers from readily sharing data, despite clear guidance that the early sharing of results is ethically demanded in emergencies, once they are quality-controlled for release, and that such early release should not jeopardise subsequent publication.[116]

Back to questions 22–26

[116] Ibid., pp33-4.