

Good participatory practice guidelines for trials of
emerging (and re-emerging) pathogens
that are likely to cause severe outbreaks in the near
future and for which few or no medical
countermeasures exist
(GPP-EP)

Outcome document of the consultative process

Executive Summary	4
1. Introduction	6
1.1 Objective of Good Participatory Practice guidelines for emerging pathogens (GPP-EP)	6
1.2 Intended audience of the GPP-EP guidelines.....	6
1.3 Scope of the GPP-EP guidelines	7
1.4 Development of the GPP-EP guidelines	7
1.5 Rationale for GPP-EP guidelines	8
1.6 Understanding, implementing, and monitoring GPP-EP	8
1.7 Organisation and how to use the GPP-EP guidelines.....	9
2. Good Participatory Practice: Definitions and Concepts	9
2.1 Who are stakeholders?	9
2.2 What is stakeholder engagement?	11
2.3 What are stakeholder advisory mechanisms?	12
2.4 The wider context of emerging pathogens.....	13
2.5 The dynamics of conducting research for emerging pathogens in crisis settings	13
2.5.1 Research and response	13
2.5.2 Relevance of Good Participatory Practice for emerging pathogen trials	14
2.5.3 Experience from Ebola trials	14
2.5.4 Trial design, ethics, and community considerations.....	15
2.5.5 Building local capacity in emergency settings	16
2.5.6 Data sharing	17
2.5.7 Management of specimens.....	17
2.5.8 Equity, power, and stakeholder engagement.....	18
3 Guiding principles and benchmarks of GPP in prevention and treatment trials for emerging pathogens.....	18
3.1.1 Respect.....	19
3.1.2 Fairness	19
3.1.3 Integrity.....	20
3.1.4 Transparency.....	20
3.1.5 Accountability	20
3.1.6 Autonomy	20
3.2 Benchmarks.....	21
3.2.1 Mutual understanding	21
3.2.2 Complementarity	21
3.2.3 Efficiency	22
4 Good participatory practice in prevention and treatment trials for emerging pathogens	22
4.1 Formative research	22
4.2 Stakeholder engagement plan	23
4.3 Communications and issues management plan	26
4.4 Protocol development.....	27
4.5 Informed consent process	29
4.6 Standard of prevention and care	30
4.7 Policies on trial-related harms	34
4.8 Trial accrual, follow-up, and exit.....	35
4.9 Trial closure, results dissemination, and post-trial access to trial products or procedures	35
Appendix 1: Acronyms.....	39

Appendix 2. Glossary.....	40
Appendix 3. Additional guidance.....	44
Members of the International Working Group on GPP-EPP	47
References	48

DECEMBER 2016

Executive Summary

The primary audience for the good participatory practice guidelines for emerging pathogens (GPP-EP) is all those involved in designing, financing, and implementing prevention and treatment trials of emerging or re-emerging pathogens. These are pathogens that are causing or are likely to cause severe outbreaks in the near future and for which few or no medical countermeasures exist. They include diseases such as Ebola virus disease, Crimean Congo haemorrhagic fever, Marburg, Lassa fever, MERS and SARS coronavirus diseases, Nipah, Rift Valley fever, Chikungunya, severe fever with thrombocytopenia syndrome, Zika, and other known and as yet unknown pathogens. This guidance specifically addresses good participatory practices during trials conducted in health emergency contexts where accelerated research processes are needed.

The limited evidence base for effectively preventing further spread of emerging pathogens and reducing morbidity and mortality for individuals, families, and communities provides a moral obligation to conduct timely research. Well-designed and well-conducted emerging pathogen prevention and treatment trials and studies are essential to discovering additional options to prevent, diagnose, and treat new infections. However, it is critical that research conducted in a health emergency actively contribute to the epidemic response and be designed to enhance long-term system capacity for both research and effective epidemic prevention and response, while respecting the rights of the involved population.

Because an emerging pathogen epidemic can negatively affect trade, tourism, national security, gross domestic product, development indicators, and citizen well-being, it is important that trial conduct not contribute to these effects. Government disaster preparedness bodies at national and regional level, leading and coordinating the epidemic response, play a central role in overseeing, approving, and monitoring the emergency research agenda and trial conduct. They are responsible for facilitating timely national scientific and ethical review processes and ensuring that trials synergize with the emergency response, while abiding to ethical and research principles including good clinical practices. By overseeing the integration of research in the national emergency response, national authorities ensure that trials contribute to the response and do not compromise it, for example, by drawing away resources that are critical for public health actions and appropriate clinical care.

Both the nature of the stakeholder pool and time constraints pose challenges to good participatory practices for research during health emergencies. However, collaborative partnering with trial stakeholders is key to building transparent, meaningful, mutually beneficial, and sustained relationships. When such relationships are respectful and address the interests of stakeholders, they underpin the conduct of scientifically rigorous and ethical trials that produce interpretable, valid data and reliable results to inform prevention and treatment strategies for emerging pathogens. Thus the ultimate goal of stakeholder engagement in a health emergency is the collective shaping of relevant, scientifically rigorous, ethical research that is in line with international standards, respects the rights of the involved population, contributes to and does not undermine the epidemic response, and leaves a sustaining legacy for the involved population.

GPP-EP is the only set of global guidelines that directly address how to engage stakeholders in the design, conduct, and conclusion of emerging pathogen prevention and treatment trials. When applied over the trial life-cycle, the GPP-EP guidelines enhance both the quality and outcomes of research. Beyond trials, they can also guide the conduct of other emerging pathogen research such as epidemiology studies, natural history studies, behavioural and anthropological research, diagnostic research, and survivor cohort studies, as well as smaller safety trials that are conducted in non-emergency settings.

The foundational GPP-EP principles underpinning partnerships among trial stakeholders in situations of crisis are respect, fairness, integrity, transparency, accountability, and autonomy while the benchmarks include mutual understanding, complementarity, and efficiency. The GPP-EP guidelines present good participatory practice for nine aspects of emerging pathogen trials: formative research; stakeholder engagement; communication and issues management; protocol development; informed consent; standard of prevention and care; trial-related harms; trial accrual, follow-up, and exit; and trial closure, results dissemination, and post-trial access to trial products or procedures.

Effective stakeholder engagement requires that trial sponsors enable GPP-EP by ensuring that research protocols include GPP-EP plans and activities, with ample budget allocation and enough time to facilitate participatory approaches, and by supporting documentation and joint publication with the community of the processes and impact of participatory approaches. Medical journal editors facilitate GPP when they require reviewers of scientific manuscripts to examine whether and how GPP-EP has been followed during trial conduct.

1. Introduction

1.1 Objective of Good Participatory Practice guidelines for emerging pathogens (GPP-EP)

The good participatory practice guidelines for emerging pathogens (GPP-EP) provide trial sponsors^a and research team members^b with principle-based guidance on how to effectively engage stakeholders in the design and conduct of prevention and treatment trials for emerging and re-emerging pathogens^c. Such pathogens are causing or are likely to cause severe outbreaks in the near future and have few or no medical countermeasures. The GPP-EP guidelines outline stakeholder engagement activities required for the development, planning, implementation, conclusion, and results dissemination of trials conducted in emergency or crisis settings.

The guidelines support greater attention to the interests of all stakeholders affected by an emerging pathogen toward a mutual understanding of meaningful stakeholder engagement in research. They help establish shared standards, expectations, and accountability for effective and outcome-driven engagement throughout all phases of emerging pathogen trials.

1.2 Intended audience of the GPP-EP guidelines

The primary audience for the GPP-EP guidelines is all those involved in designing, financing, and implementing prevention and treatment trials for emerging pathogens. This includes governments, government-sponsored research networks, non-governmental organisations, academic institutions, foundations, public–private partnerships, pharmaceutical companies, other private or public sector entities, and research teams.

The GPP-EP guidelines concern, in the first instance, diseases anticipated in the World Health Organisation R&D (WHO) Blueprint for action against epidemics(1). While it is expected that the list of priorities will be re-examined annually, the 2016 priority list includes are Ebola virus disease, Crimean Congo haemorrhagic fever, Marburg, Lassa fever, MERS and SARS coronavirus diseases, Nipah, Rift Valley fever, Chikungunya, severe fever with thrombocytopenia syndrome, Zika, and any other disease that may be so classified(2). See Box 1

Box 1

Ebola virus disease	Chikungunya	Marburg
Crimean Congo haemorrhagic fever	Lassa fever	Nipah
Rift Valley fever	MERS coronavirus	Zika
severe fever with thrombocytopenia syndrome	SARS coronavirus	

^aA sponsor is an individual, institution, company, or organisation that has responsibility for initiating, managing, or financing a clinical trial but not for conducting a trial.

^b GPP-EP guidelines are intended for all research team members, including community engagement coordinators. The latter are directly in charge of a trial site's community stakeholder engagement programme and have titles such as community liaison officer, community engagement officer, or Community Advisory Board coordinator.

^c GPP-EP is intended for trials of both emerging and re-emerging pathogens. For purposes of brevity, the term 'emerging pathogens' is used in GPP-EP.

National and local stakeholders can use the GPP-EP guidelines to monitor and evaluate stakeholder engagement efforts and to help ensure alignment with outbreak response goals to mitigate mortality and accelerate the end of an emerging pathogen epidemic.

Although the complete GPP-EP guidelines are most relevant for larger trials that have substantial impacts on individuals and populations in emergency settings, they intend to guide other types of emerging pathogen trials and studies, including epidemiology studies, natural history studies, behavioural and anthropological research, diagnostic research, and survivor cohort studies, as well as smaller safety trials conducted in non-emergency settings.

1.3 Scope of the GPP-EP guidelines

The GPP-EP guidelines provide a framework for development of effective stakeholder engagement programmes that build mutually beneficial, sustained relationships between trial sponsors and research teams and other stakeholders. When such relationships are transparent and respectful and address the interests of stakeholders, they underpin the conduct of scientifically rigorous and ethical trials that produce interpretable, valid data and reliable results to inform prevention and treatment strategies for emerging pathogens.

The GPP-EP guidelines are based on the principle that effective community engagement in research is not only an ethical imperative, it enhances the conduct of trials and contributes to robust research outcomes⁽³⁾^d. This principle-based guidance on the participatory conduct of emerging pathogen trials is intended to complement existing guidance on scientific and ethical trial conduct^e. Section 2 focuses on definitions and concepts while Section 3 presents foundational principles of GPP-EP for meaningful partnerships among trial stakeholders in situations of crisis. Section 4 outlines good participatory practices for trials conducted in emergency settings where both researchers and communities have a short window of opportunity to engage and where research must not unduly compromise but rather aim to enhance the response to an epidemic.

1.4 Development of the GPP-EP guidelines

The widely-endorsed GPP guidelines for biomedical HIV prevention trials⁽⁴⁾ (GPP-HIV)^f(11)(12)(13)(14)(15) inspired the creation of the GPP-EP guidelines. The adaptation of GPP-HIV for GPP-EP followed an accelerated process, as did the GPP guidelines for TB Drug Trials published in 2012 (16). In-depth interviews were conducted with individuals who had been involved in trials conducted during the 2014 and 2015 Ebola outbreak in Guinea, Liberia, and Sierra Leone in West

^d 'To ensure the ethical and scientific quality and outcome of proposed research, its relevance to the affected community, and its acceptance by the affected community, researchers and trial sponsors should consult communities through a transparent and meaningful participatory process which involves them in an early and sustained manner in the design, development, implementation, monitoring, and distribution of results of.....trials.' UNAIDS/WHO. Ethical considerations in biomedical HIV prevention trials 2007 [additional guidance point added in 2012].

^e Multiple guidance documents address overall scientific and ethical trial conduct, including Good Clinical Practice, Good Clinical Laboratory Practice, the Declaration of Helsinki, The Belmont Report, Guidelines of the Council for International Organizations of Medical Sciences (CIOMS), the Nuffield Council Guidance on ethics of research related to health care in developing countries, the UNAIDS/WHO Ethical considerations in biomedical HIV prevention trials, the UNESCO Universal Declaration on Bioethics, and Human Rights, and various national guidelines (see Appendix 3).

^f GPP-HIV was born out of a recommendation from the UNAIDS Creating Effective Partnerships in Research process in 2005⁽⁵⁾ that was a response to the controversies and debates about pre-exposure prophylaxis (PrEP) trials in Cambodia and Cameroon⁽⁶⁾⁽⁷⁾⁽⁸⁾⁽⁹⁾. After a series of regional consultations focused on defining the key elements needed for creating effective partnerships for biomedical HIV prevention trials⁽⁵⁾, UNAIDS and AVAC published GPP-HIV in 2007⁽¹⁰⁾. It was applied in different settings and was the subject of formal consultations with stakeholder groups in Africa, the Americas, Asia, and Europe. It began to be cited in scientific publications of the results of biomedical HIV prevention trials in 2010⁽¹¹⁾. The second edition of the GPP-HIV guidelines was published in 2011⁽⁴⁾.

Africa, including clinical trial investigators, trial site staff, anthropologists, community mobilisers, representatives of survivor groups, health care providers, ethicists, community engagement advocates, government representatives, trial sponsors, industry representatives, and other stakeholders. A review of the literature on Ebola and community engagement informed the initial draft circulated for comments to all those interviewed. An international working group examined a subsequent draft, exploring and analysing different viewpoints and areas of contention, and discussed potential objective measures of community stakeholder engagement in the design and conduct of emerging pathogen trials. The GPP-EP guidelines are dynamic and are expected to be refined further over time as experience with the conduct of clinical trials in crisis settings accumulates. **Moreover, a companion document presenting KEY ACTIONS for good participatory practices in trials of emerging (and re-emerging) pathogens – GPP-EP, is being prepared to provide a practical guide to prospective trial sponsors, investigators and other research stakeholders.**

1.5 Rationale for GPP-EP guidelines

Constructive long-term stakeholder engagement is indispensable for ensuring the ethical and scientific quality of research, its merit and relevance to local stakeholders(3), and likely uptake of interventions found efficacious. It promotes understanding of local cultures, norms and values, including concerns of vulnerable or marginalized populations, local priorities, and the dynamics of community practices that may facilitate or prevent epidemic spread. When partnerships with stakeholders are not in place prior to an emergency, following GPP-EP guidance facilitates timely stakeholder dialogue and strengthening of partnerships to help ensure that research conduct is acceptable, ethically sound, and scientifically rigorous and that it contributes to the epidemic response.

Local community and national stakeholder engagement in research design and implementation can help ensure that research questions are pertinent; trial procedures are culturally sensitive and appropriate, thus improving recruitment, retention, and adherence; and eventual uptake and use of proven research products will occur. It can help avoid reinforcing inequalities that already exist and increase the sensitivity of research staff to the needs of vulnerable populations. An essential component of stakeholder engagement is improving stakeholder knowledge and understanding of the research process by building research literacy and competencies. This, in turn, enables stakeholders to contribute more effectively to the process of guiding research and helps to address the power imbalance between research teams and community stakeholders.

Strengthening effective stakeholder collaboration fosters greater trust and respect between trial sponsors and implementers and other stakeholders. Stakeholder engagement that is transparent and mutually respectful can minimize misunderstandings and reduce the chances of unnecessary conflict or controversy. Following good participatory practice throughout a trial life-cycle facilitates local ownership of research, enables more equitable relationships, and increases the likelihood of successful research conduct, trial completion, and application of research results.

1.6 Understanding, implementing, and monitoring GPP-EP

Although implementation of the GPP-EP guidelines is a shared responsibility among all stakeholders, effective implementation proceeds only when both trial sponsors and national authorities adopt them as a requirement for successful trial conduct, monitor their implementation, and evaluate their effectiveness. This means that trial sponsors provide adequate human resources and sufficient funds in research budgets to implement the activities of Section 4 of the GPP guidelines. It also means that trial sponsors ensure that template research protocols to be used for emerging pathogen trials include plans for accelerated GPP-EP implementation during outbreaks.

Ministries of Health and other national authorities, academic institutions, ethics committees,

institutional review boards, and community stakeholders have the responsibility to support GPP-EP implementation when research is conducted in their country, institution, or area, regardless of the funding source. This includes requiring that GPP-EP plans are explicit in formal protocols and that implementation of the GPP-EP guidelines is tracked with process and outcomes documented. Reviewers of research protocols should assess the adequacy of GPP-EP plans and activities while reviewers of scientific manuscripts should examine whether and how GPP-EP has been followed during trial conduct. These assessments are facilitated when trial sponsors and medical journal editors include a specific question on GPP-EP in the forms that guide reviewers of emerging pathogen trial protocol designs or manuscripts.

Optimal monitoring of stakeholder engagement requires all stakeholders to review the GPP-EP optimal practices to determine what activities have been executed. Stakeholder engagement evaluation uses interviews, focus group discussions, surveys, or other methods to determine how stakeholders assess the impact of GPP-EP on trial conduct and stakeholder relationships. A variety of resources and tools to help stakeholders understand, implement, and monitor good participatory practice can be found at AVAC's website (www.avac.org/gpp). Oversight of GPP-EP monitoring and evaluation in health emergency settings is the mandate of the national epidemic response authorities that are aiming to ensure rapid implementation of ethical, scientifically rigorous emerging pathogen trials that follow good participatory practices.

1.7 Organization and how to use the GPP-EP guidelines

Following this introductory section, the GPP-EP guidelines are presented in three main sections:

Section 2: Definitions and Concepts defines key terms and describes the realities and underlying determinants of emerging pathogen epidemics, the context of conducting trials in emergency settings, and why a participatory approach is necessary for effective trial conduct and timely knowledge translation into practice.

Section 3: Guiding principles of GPP-EP outlines the foundational principles underpinning effective relationships among and between trial sponsors and research teams and trial stakeholders, including national response coordination bodies. These are: respect, fairness, integrity, transparency, accountability, and autonomy. Benchmarks include mutual understanding, complementarity, and efficiency.

Section 4: Good participatory practice in prevention and treatment trials for emerging pathogens describes optimal practice at each stage of the research life-cycle for the design and conduct of emerging pathogen trials in emergency settings. Nine topic areas outline expected stakeholder engagement activities, for which trial sponsors ensure sufficient funding and research teams create budgets and allocate funds:

1. Formative research activities
2. Stakeholder engagement plan
3. Communications and issues management plan
4. Protocol development
5. Informed consent process
6. Standard of prevention and care
7. Policies on trial-related harms
8. Trial accrual, follow-up, and exit
9. Trial closure, results dissemination, and post-trial access to trial products or procedures

2. Good Participatory Practice: Definitions and Concepts

2.1 Who are stakeholders?

Stakeholders are all individuals or collections of individuals who can influence or are affected by the conduct or outcome of a trial, i.e. all those who have a stake in an emerging pathogen prevention or treatment trial. They may include the population to be recruited, trial participants, families of trial participants, people living in the immediate area where the research is conducted, local survivor groups or networks, people resident within or surrounding the area affected by the emerging pathogen epidemic, religious leaders, opinion leaders, media, local health-care authorities, health care providers, traditional healers, local non-governmental organizations (NGOs), community-based organizations (CBOs), and community-based women's groups and youth groups. Trial stakeholders include those responsible for coordinating the response to the emerging pathogen, emergency response teams and other implementers, national research organisations and scientific councils, Faculties of Medicine and Nursing, and Ministries beyond Health, such as Justice, Science, Education, and others.

During a health emergency, disaster response bodies at national and regional level are critical research stakeholders as they play a central role leading and coordinating the epidemic response. They are responsible for approving and monitoring research conduct in order to avoid duplication and ensure that trials contribute to the response and do not compromise response efforts by, for example, drawing away critical resources for public health actions and appropriate clinical care. Because an emerging pathogen epidemic can negatively affect trade, tourism, national security, gross domestic product, development indicators, and citizen well-being, it is important that trial conduct not contribute to these effects.

As illustrated in Figure 1 below, a subset of stakeholders can be described as community stakeholders. They are individuals and groups that ultimately represent the interests of people who would be recruited to participate in a trial, others locally affected by conduct of a trial, and those who will be affected by the research results, including lay residents of a local area, health practitioners, service providers, and local policymakers(17). Of note, women are key community stakeholders because of their intrinsic rights and their roles as informal caregivers, as patients who may or may not be pregnant, and as community members whose opinions may be sought but not easily obtained without specific effort. Furthermore, specific attention is required to ensure that the interests of children and adolescents are represented. Trial sponsors and research teams, as well as government bodies or representatives of high-level authority structures who may be gate-keepers to access to communities, are trial stakeholders but are not generally considered to be community stakeholders.



Figure 1 Emerging pathogen trial stakeholders

In emerging pathogen epidemics in crisis situations, there may be no readily available or long-term established non-governmental or community-based organisations with research experience. It may be necessary for government to establish emergency community expert groups for joint and expedited community participation in protocol review and trial design. Such groups can provide advice on stakeholder engagement for all research and trials pertaining to an outbreak that are proposed to take place in a country. Sustaining these mechanisms helps ensure readiness to address future epidemics.

2.2 What is stakeholder engagement?

Sustained, collaborative partnering with stakeholders is key to good participatory practice and the building of transparent, meaningful, and mutually beneficial relationships. The ultimate goal of stakeholder engagement in a health emergency is the collective shaping of relevant, scientifically rigorous, ethical research that is in line with international standards, contributes to and does not undermine the epidemic response, and respects the rights of and leaves a sustaining legacy for the involved population.

Successful stakeholder engagement requires a broad, inclusive, and multifaceted understanding of the context in which an emerging pathogen prevention or treatment trial is conducted. Identification of potential stakeholders is a process that is ongoing over the life of a trial, given that stakeholders' interests, priorities, perspectives, and cultures may change. Stakeholder engagement starts with the national and local outbreak response authorities that have responsibility for ensuring that trials and other research are aligned with the emergency response. This is at the stage when research teams begin to define a problem, design a trial, determine the trial population to be recruited, and consider possible trial sites. They then consult with known local stakeholders, beginning with those who will be potentially affected at trial sites, and expand the stakeholder circle to include important community stakeholders who might be missed through a more traditional approach focused only on recognised community leaders. Reaching out to informal key opinion leaders and others who can make valuable intellectual contributions to the design of a trial is critical at this early stage. Ultimately site selection is proposed by the research team but is the final responsibility of national governments(18), advised by their epidemic response coordinating bodies.

Stakeholders will have diverse perspectives and some will have competing interests and/or power imbalances within their groups. Differences in social organization, hierarchies, gender issues, and relative social and economic status have the potential to create division and disagreement among stakeholders. Early engagement of relevant stakeholders in an honest, transparent manner that respects all parties is key to finding common ground and addressing any opposition or disagreement among stakeholders from the outset and over the course of a trial.

Stakeholders in the conduct of an emerging pathogen trial can learn from other fields that have successfully adopted participatory research approaches when researchers sought to engage with community stakeholders as equal members, sharing control over the entire research process(17)(19)(20)(21)(22)(23)(24)(25).

2.3 What are stakeholder advisory mechanisms?

Stakeholder advisory mechanisms are approaches, strategies, or structures that facilitate meaningful dialogue between research teams and relevant stakeholders about planned or ongoing clinical trials. They provide trial sponsors and research teams with information about relevant stakeholders' perspectives on the design, planning, and implementation of a specific clinical trial and facilitate open communication about research goals, processes, and results. Stakeholder advisory mechanisms, which may be informal^g or formal^h, provide relevant stakeholders with opportunities to engage with research teams during the entire life cycle of a trial. They facilitate ongoing dialogue for timely input and feedback on challenges such as consent processes(26)(27) and other issues arising throughout a trial. In most crisis settings, there may be no existing research stakeholder advisory mechanism and one will need to be built and sustained throughout the trial's duration. Close liaison with stakeholder advisory mechanisms set up for the emerging pathogen response promotes open communication and joint monitoring to ensure that trial conduct contributes to the response.

A community advisory board (CAB) composed of individuals or stakeholder representatives is a stakeholder advisory mechanism intended to provide an independent advisory voice. It meets regularly with research team representatives, informs community stakeholders about proposed and ongoing research, and provides feedback to research teams about local norms and beliefs, as well as local views and concerns that arise in specific trials. CAB composition is intended to reflect the diversity of community stakeholder interests and needs with respect to proposed or ongoing research. CABs may include members or representatives of the surrounding area, individuals in the population from which participants will be recruited, survivors and their families, current or former trial participants, religious or opinion leaders, and representatives of other sections of society as determined by the trial's location and eligibility criteria. Careful consideration needs to be given to the range of stakeholder advisory mechanisms that are required to best support effective engagement. Establishing a CAB takes time and may be helpful but it is not sufficient for gaining adequate and appropriate community stakeholder input for emerging pathogen research in crisis

^gInformal stakeholder advisory mechanisms may be events or less formal means that assist research teams in learning about relevant stakeholders' views on proposed or ongoing research. Examples include stakeholder meetings, local events, focus group discussions, interviews, consultations, and suggestion boxes. Participants may include individuals and representatives of existing organizations, local employer associations, local government or traditional committees, and other advocacy, charitable, cultural, political, religious, or social groups.

^hFormal stakeholder advisory mechanisms typically involve established groups that develop an ongoing relationship with the research team at a particular trial site. Examples include: trial participant groups (former or current participants), professional groups (local scientists, health care providers, local media, or experts on local socio-cultural issues), government-convened research coordination meetings, non-governmental organization advisory groups (with representatives from different non-governmental organizations or community-based organizations), and community advisory boards.

settings.

2.4 The wider context of emerging pathogens

The occurrence of emerging pathogens, likely to cause severe outbreaks in the near future and for which few or no medical countermeasures exist, is an increasingly tangible risk in an interconnected world where goods, people, and vectors travel globally. Population growth, trade and other economic factors, and climate change are combining to bring the natural habitats of animals closer to humans and to change the geographic range of insect vectors, resulting in rising probabilities of human exposure to emerging pathogens.

Structural determinants may create, enhance, and perpetuate the risk that a known pathogen will re-emerge or that a novel pathogen will jump species and spread rapidly. They include poverty and inequity, civil conflict and war, natural disasters, lack of early-detection disease surveillance systems, under-resourced health systems resulting in weak infrastructure for a timely response(28), and disregard of international health regulations.

Emerging pathogens can spread for some time in human populations before they are detected. Delayed and inadequate responses to emerging pathogen risks are characterised by, among other things, poor communication, misconceptions of disease and disease causation, lack of knowledge of local customs and culture, and community reluctance to participate in the response because of historical or newly generated distrust, compounded by ill-informed community engagement strategies(29).

2.5 The dynamics of conducting research for emerging pathogens in crisis settings

2.5.1 Research and response

An emerging pathogen outbreak can accelerate a product pipeline, stimulate early phase studies of vaccine candidates or therapeutic products, and quicken the pace toward efficacy trials for candidates that have already gone through early phase trials. Generating knowledge quickly, maintaining public trust, and addressing the practical challenges of conducting scientifically-valid research ethically in a crisis situation all need to be carefully balanced(30). In addition to clinical trials evaluating experimental treatments, vaccines, and other preventive measures, research on diagnostics, natural history, epidemiology, anthropology, human behaviour, and implementation strategies can play a critical role in reducing morbidity and mortality and mitigating the social and economic consequences of an outbreak (31). Research can be facilitated by promoting regulatory convergence among countries; pre-approval of clinical trial designs; and mechanisms to manage intellectual property, data sharing, and product liability(32).

Outbreaks of emerging pathogens can occur in the context of relatively well-developed health systems(33)(34)(35)(36)(37)(38)(39). In resource-constrained settings, extremely limited health infrastructure may already be hampering the public health response to an emerging pathogen at the time that a clinical trial is proposed. External resources may flow in to such settings in order to compensate for inadequate numbers of health service personnel, build laboratory capacity, and create new buildings to isolate and house people who are infected. Although the limited evidence base for effectively preventing and reducing the impact of an epidemic provides a moral obligation to conduct research, it is essential that research not undermine but rather actively contribute to the response. Both the response and any trials undertaken should be designed to enhance long-term system capacity for effective epidemic prevention and response.

With few or no medical countermeasures available to respond to an epidemic, trials may be viewed

by people anywhere in the world as potentially life-saving for those already infected. This may be the case not only because of hope that the active product may have therapeutic benefit, known as *therapeutic misconception*(40), but also because trial participants in any country may be perceived to receive or may actually get better supportive care, regardless of which trial arm they are in.

2.5.2 Relevance of Good Participatory Practice for emerging pathogen trials

Creating spaces in which people can speak about their fears and concerns, share their views about research, and be heard is an essential component of good participatory practice. This is true whether, for example, healthy volunteers are to be recruited in phase I vaccine trials, ill and dying patients are to be recruited for therapeutic trials, or experimental manipulation of a vector such as *Aedes aegypti* in the community is planned. Without effective stakeholder engagement, research on emerging pathogens can encounter significant hurdles at any stage from design and approval to conduct and results dissemination.

Formative research (see Section 4.1) constitutes the initial phase of stakeholder outreach and engagement. In settings where little research has been conducted, research literacy may be low, clinical trial literacy may be even lower, and the hostility of the population may be high. Local anthropologists; researchers in agriculture, hydrology, and other domains; and health, social service, and other providers may be best placed to advise on channels of communication, local power dynamics, and community decision-making. In multi-ethnic communities, care needs to be given to representing the voices of all ethnicities in discussions of trial design and conduct. To complement local research teams, consideration can be given to involving international researchers who have an overarching perspective and deep knowledge of the country, although this may increase distrust(29). The formative research phase has to be nimble and quick in an emergency setting, building on stakeholder engagement in the emerging pathogen response to identify key voices to participate from the outset in discussions of trial design. The window for conducting research may be short if the epidemic response is effective, further necessitating rapid identification of relevant trial stakeholders.

Formulating stakeholder engagement plans (see Section 4.2) and communications and issue management plans (see Section 4.3) is key to anticipating risks and managing these effectively. Research stakeholders in crisis settings may include, for example, health care workers and other frontline care providers, who are themselves at risk(41). Throughout a trial, they are in a position to hear concerns about the trial, provide correct information if their own questions about the research have been addressed, report persistent rumours, and assist in developing plans to mitigate the impact of falsehoods on trial conduct.

Discussions with epidemic response coordination bodies and with national and local health authorities are essential for implementation of standard of prevention and care provisions agreed by all stakeholders (see Section 4.6). Key government decision-makers at all levels involved in the epidemic response need current information on trial progress through regular face-to-face meetings, briefing notes, and media talking points. In emergency settings, the local business community may constitute an influential trial stakeholder. Rival scientific peers may constitute important foes of a trial if they are not informed and their concerns addressed early in the research process. Local media are key partners in the dissemination of correct information about a trial. Because engaged and effective community advisory mechanisms are an essential element of good participatory practice throughout emerging pathogen prevention or treatment trials, making every effort to establish them from the outset will strengthen trial conduct.

2.5.3 Experience from Ebola trials

Ebola was not a new disease in 2014, having been recognised as early as 1976(42)(43). Because several candidate products had already undergone preclinical and some clinical studies, further pre-clinical studies and Phase I, Phase II and Phase III trials got underway quite quickly, alongside the response(1). However, community engagement activities for the response to Ebola had not been fully implemented in many settings when research began to be proposed. Fear, panic, and rumours at times spread faster than the truth. They were reported among participants in Phase I and II Ebola vaccine trials in Liberia(44) and completely disrupted a Phase I Ebola vaccine trial proposed for conduct in an unaffected population in Ghana(45). These examples highlight the importance of effective stakeholder involvement at the trial design stage.

A treatment trial in Guinea undertook an active researcher-stakeholder engagement process in the conceptualisation phase, resulting in the design of a historically controlled, single-arm proof-of-concept study, rather than a randomised controlled trial(46). Stakeholders involved in the response on the ground argued that the high mortality rate of the disease would make it unethical to randomise patients in the same family or village seeking care. However, this design meant that the trial was unable to draw conclusions on the usefulness of the experimental drug favipirivir. For a vaccine trial (ChAd3-ZEBOV/ VSV-EBOV) conducted in Liberia, the government placed the research response under the guidance of an incident management system and assigned a group of Liberian scientists to work with US scientists on trial design. They recommended use of a saline rather than active placebo and social mobilisationⁱ and communication strategies that resulted in expedited research initiation four months following initial partnership formation. The trial's social mobilisation strategy promoted the trial, enhanced enrolment of consenting participants, and included a community engagement pillar, the prime goal of which was to encourage study participation(44). The Phase I vaccine trials conducted in Geneva, Hamburg, and Kilifi, Kenya may not have had any formal community advisory mechanisms(47), however there were extensive local discussions about the trial with stakeholders. In Guinea, the community was clearly committed to defeating Ebola(48) and 95% of the study staff of the successful ring vaccination trial (49)(50) were from Guinea. Prior and during the trial, extensive discussions were held with religious leaders, leading with full support for the trial by the community. Importantly, the Conakry Imam issued a Fatwa in support of continuing ring vaccination activities – including active immunization – during the 2015 month of Ramadan. In Sierra Leone, formative research was conducted before implementation of Phase 1 and 2 trials that incorporated both social science and community liaison teams(51).

The extent to which there has been effective community stakeholder engagement, including formation of community advisory mechanisms, in Ebola trials has not been well documented. Where it was lacking in reality, this may have resulted from the perception that the emergency footing of these trials precluded it. Some research teams and sponsors may have misconceived social mobilisation aimed at raising awareness and enhancing recruitment as constituting meaningful community involvement. Although active engagement of community stakeholders in the design and conduct of a trial appears to have been the exception rather than the rule, there is some evidence that this improved over time. Good participatory practice is all the more needed in communities with low research literacy(52) to mitigate against research exploitation; shape study design, informed consent processes, and trial implementation; and establish provisions for post-trial access.

2.5.4 Trial design, ethics, and community considerations

Debate among researchers about appropriate designs for trials to be conducted in emergency settings has been intense(53). Randomised controlled trials for vaccines are considered to be

ⁱ Social mobilisation is defined generally as a process that raises awareness and motivates people to demand change or a particular development. See: <https://www.reference.com/world-view/social-mobilization-9a02bbf5e1843a99>

ethically acceptable if it is unclear whether a vaccine will help, cause harm, or do nothing. However, in emergency settings with hundreds of health care workers and other frontline caregivers at risk for occupational exposure, it may be ethically unacceptable to randomise personnel to a placebo arm when a vaccine candidate has shown promise in animal experiments. Alternative study designs for vaccine trials have included using a proven vaccine such as hepatitis B vaccine in the control arm and conducting a stepped-wedge trial in which everyone eventually gets the experimental vaccine, with attack rates compared among those already vaccinated and those waiting to be vaccinated. Adaptive trials may start with a number of products and remove arms that are found less promising at frequent interim analyses, in an attempt to balance urgent therapeutic needs with the regulatory imperatives of generating sound safety and effectiveness data(54). The open-label cluster-randomised ring vaccination trial randomised clusters (or rings) of contacts and contact-of-contact of cases to immediate or delayed (21 days later) vaccination(49). Doing so allowed the trial to conclude on the efficacy and effectiveness of the vaccine (comparing number of Ebola cases in ring vaccinated immediately with those occurring in rings randomised to delayed vaccination), while not withholding access to a potentially effective vaccine to the control group for more than three weeks.

Therapeutic trials face the issue of providing enhanced standard of care in all trial arms, as usual standard of care may not be considered ethical. With sick and dying patients and a high case fatality rate, there may be pressure to provide compassionate access(55) to experimental drugs that have shown promise in animal studies. However, the fact that drug candidates can show impressive results in animal models and then fail in randomised human studies is well-known(56). Agents being tested in therapeutic trials generally have promising animal data but they may have no effect, be beneficial, or create harm in humans. Communicating this equipoise poses challenges and there may be strong pressure to avoid placebo-controlled designs in favour of study designs that may or may not produce interpretable, valid, and replicable results(56). Importantly, the factors that affect the perceptions of researchers and sponsors about the acceptability of a trial design(57) may be quite different to those influencing the views of other stakeholders in a crisis setting, including those of the community. Furthermore, the conduct of trials that are unable to draw scientific conclusions may be considered unethical.

A key concern of all stakeholders is the ethical imperative to provide post-trial access for trial participants, their families, and their communities, in the first instance, to any prevention or therapeutic product scientifically proven beneficial, even before full licensing approval (see Section 4.9). Regulatory coordination, to align expectations across jurisdictions on the burden of proof for product review and approval, informs appropriate trial design and helps ensure the quality and safety of needed products for rapid deployment in public health emergencies(56).

Obtaining informed consent for participation in a clinical trial being conducted in a crisis situation is not straightforward (see Section 4.5). The decision to participate in a clinical trial is an individual right. In some settings, a person's good health may be considered a family or communal asset, with familial or communal approval required before an individual can decide whether or not to provide her or his consent to trial participation. What to do about the participation of sick children and adolescents who lack guardians to provide consent is a key question for discussion with community stakeholders and ethics committees. In the case of vaccine trials, obtaining phase I/II safety data in children within ongoing adult trials(58) would allow rapid bridging of efficacious vaccine candidates to paediatric populations. For example, upon requests from both the National authorities and the communities where vaccination was taking place, the ring vaccination trial protocol was amended to include children aged 6 years and older based on preliminary unpublished data from phase I trials in Gabon(59).

2.5.5 Building local capacity in emergency settings

When a trial is conducted in a crisis situation, there may be pressure to expedite trial protocol approval by scientific, ethical, and regulatory bodies. Assessments may need to be conducted in parallel. The volume of proposals being presented to these bodies may overwhelm them, in the absence of assistance in prioritisation from national and regional emergency response authorities overseeing the alignment of research within the epidemic response. Strengthening review mechanisms, alongside health care and public health infrastructure, is a clear priority. Capacity building of regulatory and ethical bodies may be considered a conflict of interest if it is financed by submitting trial sponsors. Ideally, a mapping now by countries and the global community of potential hotspots for emerging pathogens would allow strengthening of clinical trial infrastructure in anticipation. If governments, researchers, private industry, nongovernmental organisations, and other stakeholders develop a framework of norms and rules operating during and between outbreaks, this will enable and accelerate research, govern research conduct, and ensure access to the benefits of research(32). Such a framework would usefully be developed alongside updating of national public health laws, strengthening of early warning and surveillance mechanisms, and developing organised systems for ethical oversight of public health activities(31).

Likewise, work to build research literacy and understanding of trial conduct among community stakeholders, scientific peers, local media, and the general population would expedite the initiation of GPP-EP for trials in crisis situations. It would make clear that community engagement is not about recruitment, but rather about emancipating communities to actively engage with research as well-informed, equal partners. Building these competencies would create a crop of research-literate, trusted people in communities who are ready to engage with study design and implementation during emergencies.

2.5.6 Data sharing

Public health action in unfolding health emergencies requires rapid data sharing and dissemination by researchers to fellow researchers and to stakeholders. Protocols and analysis plans for clinical trials conducted in the context of public health emergencies should include an explicit expedited timeline commitment for sharing clinical trial data and results(60). As opting in to data sharing becomes the new default practice, researchers are responsible for the accuracy of shared preliminary results, ensuring that they have been subjected to sufficient quality control before public dissemination(61). WHO's *Zika Open* collection allows public scrutiny and unrestricted use of data while Zika-related manuscripts are undergoing peer review(62). Good participatory practice for data sharing was lacking in the Ebola crisis. It was not always standard practice to hold confidential conference call briefings involving all Ebola vaccine trial researchers or all Ebola therapeutic trial researchers to explain a relevant trial's results prior to public dissemination. Community stakeholder briefings to avoid communities learning of results first through the media appear not to have taken place in the first instance for any of the Ebola trials (see Section 4.9.C.2).

2.5.7 Management of specimens

Rumours that blood, body parts, and other research specimens are being sold can spread rapidly in the absence of effective early communication about the management of specimens, including their safe storage and disposal. Concerns about specimens leaving the country can arise in the absence of formal material transfer agreements documenting the purpose, informed consent provisions, confidentiality protections, specimen physical biosecurity, and guarantees that the country of origin will be acknowledged and any eventual benefits shared with the communities from which the samples were obtained(31), if the outbreak recurs. Transparency about specimen ownership and why needed laboratory studies cannot be performed in the country is important. Anticipating and initiating laboratory capacity strengthening for future outbreaks can help prevent future controversies about specimen management and ownership in a crisis situation.

2.5.8 Equity, power, and stakeholder engagement

Power inequalities exist between research sponsors and funding recipients with respect to a range of issues, such as decision-making processes, priority setting, control of resources, and equitable recognition of input. With projected market failure for the private sector, most prevention and treatment trials for emerging pathogens are funded by institutions in high-income countries and conducted with multiple partner institutions, including those in low- and middle-income countries. Disparities among these institutions and partners can introduce or reinforce power inequalities among trial sponsors and implementers that can translate into inequalities between trial implementers and other stakeholders.

Conducting trials in multiple settings and countries introduces another level of complexity. Variation in cultures, physical environments, infrastructure, research experience, health policies, and national laws can introduce inequalities among research teams and between research teams and site-level community stakeholders. Sociocultural aspects, which can be complex and nuanced, may create potential challenges for trial implementation⁽⁶³⁾ but may also serve as points of resilience or community strength for trials to draw upon⁽⁶⁴⁾.

Power inequalities between research teams and community stakeholders can include imbalances in literacy, education, and economic resources as well as those inherent in patient–provider relationships. National, racial, ethnic, and linguistic differences between members of research teams and community stakeholders can exacerbate inequalities. Recognition of these factors is the first step to developing practices that avoid inadvertently replicating or reinforcing them in the design and conduct of emerging pathogen prevention and treatment trials.

Experimental options are optimally tested for safety and effectiveness in populations that need these interventions the most and are likely to benefit from them should they prove effective. However, the very factors that increase risk in such populations may contribute to increased vulnerability to exploitation. It is important to recognise the implications of such social justice and human rights issues for research conduct in emergency settings.

There are many inherent complexities in conducting emerging pathogen prevention and treatment trials in crisis situations. By acknowledging and understanding these challenges, trial sponsors and implementers can more appropriately and effectively facilitate a mutually beneficial, participatory approach to trial conduct that strengthens local research capacity at all levels. Stakeholder engagement helps emancipate and equip community stakeholders to engage meaningfully in the research process, counterbalance inequalities, and harness the expertise that they can contribute to the design and conduct of research.

The lessons learned from research conducted during the response to the 2014-2015 Ebola epidemic have informed development of GPP-EP guidelines for future trial conduct of emerging and re-emerging pathogens considered in the WHO Research and Development Blueprint⁽⁶⁵⁾, as well as other known and currently unidentified pathogens likely to cause outbreaks in the near future.

3 Guiding principles and benchmarks of GPP in prevention and treatment trials for emerging pathogens

The principles and the benchmarks of good participatory practice form the ethical framework that guides research teams and stakeholders as they plan and implement their stakeholder engagement programme throughout the life cycle of an emerging pathogen trial conducted in a health emergency. The principles reflect a set of values that are fundamental to initiating and sustaining partnerships and ensuring that collectively-identified goals are achieved in the crisis contexts in which trials for emerging pathogens are conducted. The benchmarks are outcomes that can play a

useful role in the development of monitoring and evaluation indicators. As experience with GPP-EP implementation increases, additional relevant principles and benchmarks to evaluate stakeholder engagement programmes will be identified. Figure 2 summarises the current principles and benchmarks.

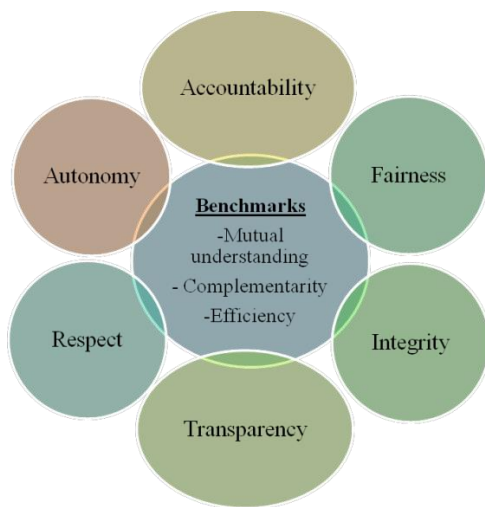


Figure 2. The principles and benchmarks underlying the GPP-EP.

Under some circumstances, the considerations that are part of the GPP-EP ethical framework may need to be weighed against each other through a deliberation process in which all stakeholders are heard, interests are balanced, and options are pursued for mutual gains tailored to local circumstances. Deliberation entails formal discussions among stakeholders who have a legitimate interest in the consequences of a trade-off between considerations. For example, deliberation might be necessary in order to include pharmaceutical products from different drug companies in a single trial or to address remuneration for participation in the stakeholder engagement process. In the latter case, notions of respect might suggest that participants should be compensated for their time when taking part in an advisory mechanism, while the principle of autonomy might suggest differently.

3.1.1 Respect

Respect among stakeholders is key to communicating effectively, fostering trust, and developing partnerships to achieve collectively-set goals. Respect is demonstrated when stakeholders communicate and act in ways that value and honour each other's perspectives and realities and are responsive to each other's interests. In an emergency context, mutual respect is essential for aligning research efforts with the outbreak response. Ethical research requires fundamental respect for human rights and for the confidentiality of trial participants and their information. It also requires respect for local values, cultures, and perspectives, as well as respect for the scientific process.

3.1.2 Fairness

In the context of stakeholder engagement, fairness refers to the way that stakeholders communicate with and treat each other. The notion of fair dealings emphasises honest acknowledgment of one's own interests and motivations, avoiding any active or passive deception when communicating with other parties. During the engagement process, no group of stakeholders should privilege their own interests arbitrarily over those of any other groups, based on having greater power, influence, access to resources, or knowledge. The principle of fairness takes on particular importance when trial

sponsors and research teams seek to establish a dialogue with health authorities and with trial populations that might be more vulnerable and require special attention.

3.1.3 Integrity

Integrity generally refers to choosing actions that are consistent with one's values and reliably living up to commitments and promises on the terms that they were made. For research stakeholders, this means representing their own constituency's interests even when this will entail intricate back and forth discussions with other stakeholders. Maintaining the highest standards of scientific and ethical integrity is a driving force of the engagement process even in the context of an outbreak. Scientific integrity requires adherence to scientific processes that meet the highest scientific standards and achieve valid, interpretable results. Ethical integrity requires adherence to universal ethical principles that include respect for persons, autonomy, beneficence, and justice(66). Both scientific and ethical integrity are fundamental to achieving the scientific goals of a trial, maximising trial benefits for community stakeholders, and advancing science on emerging pathogens globally.

3.1.4 Transparency

Open, honest, timely, and clear communication is a hallmark of transparency and fosters collaborative, trusting, and constructive relationships. Transparency requires operating in such a way that it is easy for parties to understand each other's interests; to see what actions are being proposed, planned, or performed; and to understand the relevant lines of authority and accountability. Transparency about the research process includes ensuring that stakeholders have truthful, complete, and understandable information about a trial's objectives and processes. It means ensuring that feedback from a broad range of stakeholders is acknowledged and addressed, and that they receive feedback in turn on how their issues were handled. Transparency includes ensuring clarity on the respective roles and responsibilities of stakeholders; the constituents, if any, that they represent; and the extent to which their input may influence trial-related decisions. Adherence to the principle of transparency means that stakeholders communicate readily with research teams, and vice versa, about changing circumstances that may affect previously-agreed levels of consultation, involvement, collaboration, and decision-making.

3.1.5 Accountability

Accountability is fundamental to sustaining relationships built on trust and mutual respect. Trial sponsors and implementers are accountable to society at large for conducting scientifically valid and ethical research and for their participatory practice, including responses to input from relevant stakeholders as mutually agreed. They are accountable for ensuring that funding is adequate to enable optimal engagement between research teams and other stakeholders. They are accountable to national and local epidemic response coordinating mechanisms.

Community stakeholders and other relevant stakeholders are accountable for ensuring that their input into the research process is fair and constructive, respects the scientific process, and is in the best self-identified interests of community stakeholders. Those who accept responsibility to act as liaisons or representatives between research teams and other stakeholders are accountable for representing the interests of those they represent, sharing information about planned or ongoing trials with them, and expressing their needs and concerns to research teams.

3.1.6 Autonomy

Autonomy in the context of stakeholder engagement recognises stakeholders' entitlement to support, amend, or refuse proposals to conduct research in a particular area, depending on their self-identified interests and desires. In efficiently addressing evidence needs for an outbreak response, national and local response structures may prioritise some trials over others. Adding

complexity, different stakeholders may have divergent perspectives on the relevance or appropriateness of a specific trial. The principle of autonomy also refers to the independence of community advisory mechanisms put in place to elicit feedback from community representatives. For instance, CABs created as part of a specific trial are accountable to the constituencies they represent, even if they receive funding from entities organising a trial. Such entities are responsible for ensuring that advisory mechanism terms of reference are clear with respect to autonomy.

Autonomy at all levels for informed decision-making about a specific trial is dependent on understanding the local, national, and global risks and benefits associated with trial implementation, particularly in the context of an outbreak. Engaging local media as part of the communications and issues management plan early in the trial design process (see Section 4.3) is key to ensuring that correct information is provided to all stakeholders to assist them in making decisions.

3.2 Benchmarks

3.2.1 Mutual understanding

A common understanding about each other's interests in a trial and about the research objectives and how to achieve them requires that all stakeholders improve their knowledge, skills, and competencies in both socio-cultural issues and the meaning and significance of various research processes.

Socio-cultural competency includes understanding the norms, practices, and beliefs of relevant cultures; social circumstances; diverse stakeholder perspectives on research and research priorities; and implications of power differences among stakeholders. Building socio-cultural competency enables collaboration among stakeholders with diverse backgrounds and priorities and it informs the development of appropriate trial designs and procedures.

Research competency includes understanding the scientific process of defining research questions, developing appropriate trial designs, collecting and analysing data to ensure valid results, and disseminating findings. Building research competency enhances understanding of the concepts, purposes, practices, limitations, and results of clinical trials and enables and emancipates communities and other stakeholders to provide sustained, meaningful input into the research process.

At the start of a trial's design phase, a principal investigator new to a particular location may have high research competency but low socio-cultural competency while a community stakeholder new to research may have high socio-cultural competency but low research competency. All trial stakeholders share ongoing responsibility to review and strengthen their sociocultural and research competencies in order to improve mutual understanding.

3.2.2 Complementarity

Complementarity implies that stakeholder interactions produce an effect that is greater than the sum of individual contributions. It means that trial sponsors, research teams, and local public health systems all strive to maximise the impact that both research and health care have on local populations. Such synergy is achieved when emerging pathogen research is aligned to the evidence needs of the outbreak response. Enabling the response means ensuring that research does not compete with the public health system for human resources and that infrastructures built for the trial, including communication networks for effective reporting and monitoring of identified emerging pathogen cases, use standards relevant for the local health system. Complementarity with community research stakeholders is manifested in better understanding of the disease, higher recruitment, more efficient use of limited resources, and trial completion. Better outcomes are likely

when all stakeholders see themselves as partners achieving the most advantageous trial conduct for all.

3.2.3 Efficiency

Emphasising efficiency as a benchmark of GPP-EP underscores the importance of maximising resource use and minimising waste of time in order to accelerate research that meets the needs of the outbreak while addressing relevant scientific questions before the outbreak declines. Although the paucity of available data about the cost-benefit of specific engagement activities may hamper an efficiency-based selection of stakeholder engagement approaches, abiding by GPP-EP principles for sustaining effective partnerships is the most promising way for trial sponsors and research teams to strive for programme efficiency until monitoring and evaluation data become more readily available.

4 Good participatory practice in prevention and treatment trials for emerging pathogens

The design, planning, and implementation of clinical trials are guided by a range of standards such as *Good Clinical Practice*,⁽⁶⁷⁾⁽⁶⁸⁾ *Good Clinical Laboratory Practice*⁽⁶⁹⁾, and *Good Manufacturing Practice*⁽⁷⁰⁾. This section describes a systematic framework for *Good Participatory Practice* that trial sponsors and implementers can adopt and use to develop effective partnerships with relevant stakeholders in planning and conducting trials, as well as in monitoring good participatory practice. Appropriate and meaningful stakeholder engagement occurs at all stages of the research life cycle—from trial conceptualisation to results dissemination. This section describes stakeholder engagement processes in the general sequence in which they may occur, although these processes are not necessarily sequential or time-limited and can take place as parallel, overlapping, or ongoing activities. Application of each practice or set of practices will vary by location, the type of trial being conducted, and trial site experience with respect to previously established stakeholder engagement programmes and activities. Nine elements of the trial life-cycle are discussed under three subsections: A. definition and relevance to good participatory practice, B. special considerations, and C. good participatory practice.

4.1 Formative research

4.1.A Definition and relevance to good participatory practice

Formative research activities enable research teams to gain an essential understanding of local population socio-cultural norms, practices, and traditions; local power dynamics; local perceptions; channels of communication and decision-making; and the local history of research. In the context of health emergencies, where time is of the essence, there may be considerable pre-existing research about local values and beliefs that can help identify the needs and priorities of people who are locally affected by and able to influence the trial. The outbreak response may already include structured efforts to engage and inform the community. Research stakeholders can collaboratively leverage these to avoid duplication of efforts. Formative research activities usually constitute the initial phase of stakeholder outreach and engagement, the outcome of which influences the conceptualisation of a clinical trial. Engaging community stakeholders to develop research questions, gather information, and analyse results from formative research activities provides researchers with opportunities to initiate discussions with potential trial sites and create community awareness about the proposed research. Working together on formative research builds trust and lays the foundation for effective engagement.

4.1.B Special considerations

1. Although information may be gathered informally about local populations and research areas, formal formative research activities require protocols that are ethically and scientifically

reviewed and approved by the national response. In the context of health emergencies, formal formative research that takes place either before an outbreak or is expedited will facilitate rapid trial deployment to assist the epidemic response.

2. While new trial sites may require extensive formative research activities, experienced trial sites may benefit from focused activities to gather stakeholder feedback regarding previous trials, evaluate ongoing research partnerships, and consider any changes in the local context that could influence trial design and implementation. Experienced trial sites may also benefit from extensive formative research activities if the clinical trial involves the use of products, systems, or structures new to the research site or if the proposed trial will recruit from a new location or population.
3. In the context of a declared public health emergency of international concern (PHEIC), as well as in a localized outbreak that may not qualify as a WHO-declared PHEIC, there may be considerable fears, myths, and misconceptions among affected families, health care providers, traditional healers, political decision makers, and others in the general population. Acknowledging these fears and concerns is the first step to gaining understanding and initiating conversations about the conduct of a clinical trial to test an experimental prevention or treatment product when few or no medical countermeasures exist.
4. The negative impacts on the whole community of pre-trial formative research findings and of socio-behavioural research conducted alongside a clinical trial are minimized and positive impacts enhanced if findings are routinely included in discussions with stakeholders as part of adherence to GPP-EP principles and for iterative learning.

4.1.C Good participatory practice for formative research activities

1. Research teams identify skilled and competent key informants and relevant stakeholders to assist in planning, implementing, and reviewing the process and results of formative research activities (see also Section 4.2 on stakeholder engagement).
2. Research teams designate trial site staff responsible for managing formative research activities. A social scientist assists in the formulation of formative research activities and conducts social science research throughout the trial to ensure that ethical issues, acceptability experiences, rumours, and other concerns are captured. Close collaboration of the clinical, community liaison, and social science teams will ensure that findings are addressed in a timely manner, with trial processes adapted where indicated and when possible.
3. Research teams and relevant stakeholders rapidly develop a formative research protocol and discuss scientific and ethical approval mechanisms, notification processes, implementation plans, specific activities, timelines, and required resources. The protocol describes key information to be gathered and questions to be answered for effective planning and implementation of the trial, appropriate information collection methods, and the research team members and community stakeholders best-suited to collect the required information.
4. Research teams document formative research activities, including techniques used and information collected, as well as the results and their interpretation. They discuss the findings and their implications for trial design, conduct, and development of effective stakeholder engagement mechanisms with relevant trial stakeholders.

4.2 Stakeholder engagement plan

4.2.A Definition and relevance to good participatory practice

Informed by information gathering and formative research, a comprehensive and effective stakeholder engagement plan describes strategies and mechanisms for building relationships and

constructively engaging with a broad range of local, national, and international stakeholders. It enables a more participatory approach to trial conduct, helps research teams to design and implement locally acceptable research, and lays the foundation for a supportive research environment that extends beyond the lifespan of a specific trial. The plan includes establishing, maintaining, and engaging stakeholder advisory mechanisms throughout the life-cycle of a trial to ensure continuous dialogue with community stakeholders. It describes strategies and mechanisms for providing relevant education about a specific planned trial—and about research in general—in order to enhance research literacy. Coordinating with communication strategies for the emerging pathogen response, the plan for stakeholder education includes mechanisms for iterative learning in response to evolving needs. Effective stakeholder education is key to building research literacy and, ultimately, to emancipating community stakeholders as decision-making agents in trials.

4.2.B Special considerations

1. Trials for emerging pathogens may be conducted in a research-naïve area or at a well-established research facility with existing stakeholder advisory mechanisms. Being familiar with and appreciating relationship dynamics among different stakeholders in the trial community increases the research team's ability to effectively and constructively engage with a broad range of relevant stakeholders, deepens understanding of local context, and informs the development of the stakeholder engagement plan. Stakeholder identification and inclusion is facilitated by formative research but is a dynamic process, given that the stakeholder landscape varies from site to site and over time.
2. Careful thought is needed about the range of stakeholder advisory mechanisms required to best support effective participatory practice in a crisis situation. Risks may outweigh benefits in holding face-to-face stakeholder meetings when church, school, market, and social gatherings are prohibited to control disease spread or where there is risk of violence. Measures afforded to health care providers can be instituted to minimize exposure risk for stakeholders during research meetings and alternate means can be created to obtain community inputs without physical presence, for example, through social media.
3. While community advisory boards (CABs) are often funded by trial sponsors and sites, they are intended to be an independent advisory voice that is free to express concerns about proposed or ongoing research. Although they can assist research teams in designing effective trial recruitment strategies, they do not participate in implementing actual trial procedures, such as trial participant recruitment.
4. Stakeholder education enhances research literacy, fosters more equitable relationships, and positively influences trial recruitment activities but is not intended to have participant recruitment as a goal.

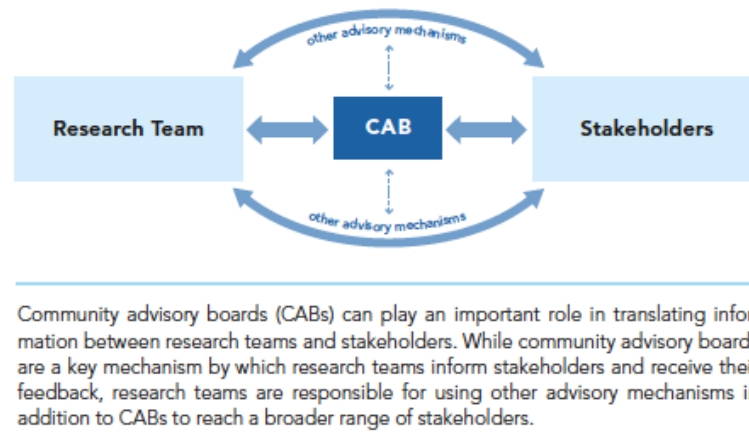


Figure 3: The role of community advisory boards

4.2.C Good participatory practice for stakeholder engagement plans^j

1. Research teams comprehensively identify relevant stakeholders (see Section 4.1) within and surrounding the research area, as well as regionally, nationally, and internationally. They map local stakeholders in order to determine which are relevant to trial implementation and key to sustained stakeholder engagement. They designate trial site staff responsible for managing activities and relationships involving stakeholder engagement planning, advisory mechanisms, and education to enhance research literacy.
2. Research teams and relevant stakeholders discuss and develop a stakeholder engagement plan to cover the trial's life-cycle. It defines the range of stakeholders to be engaged, specifically ensuring inclusion of relevant governmental, non-governmental, and community-based organisations and groups. It clarifies the type of engagement appropriate for each stakeholder, such as being informed, consulted, collaborated with, or emancipated to make decisions. It describes methods for resolution of differences of opinion. It details the frequency and type of engagement methods to be used, such as public meetings, workshops, joint decision-making models, or delegated decision-making. It describes the process by which new relevant stakeholders will be identified and engaged and the nature of support for initial and ongoing capacity-building. It outlines the frequency with which the engagement plan will be reviewed and the monitoring indicators and review criteria to be used to assess its success.
3. Stakeholder engagement plans include clear strategies for the identification, establishment, and maintenance of stakeholder advisory mechanisms, in addition to those for community advisory boards. A crisis situation calls for nimble and adaptive mechanisms for stakeholder engagement as conditions change. Research teams and relevant stakeholders work together to determine how to ensure greater and more inclusive involvement of stakeholders, including representatives of populations that will be recruited into trials. They make the development of stakeholder advisory mechanisms transparent to community stakeholders. On an ongoing basis, they review the composition of existing mechanisms and the need for new advisory mechanisms to ensure that relevant stakeholders continue to be represented during the course of a trial.
4. Research teams and relevant stakeholders determine the purpose and scope of each formal stakeholder advisory mechanism. This may result in establishing terms of reference or by-laws

^j Additional guidance: Recommendations for Community Involvement in National Institute of Allergy and Infectious Diseases HIV/AIDS Clinical Trials Research(71).

that define responsibilities, such as the responsibility to develop, review, discuss, and provide input on relevant trial documents and procedures. They determine the structure of each stakeholder advisory mechanism and any guidelines about electing a chairperson and defining the duration of service for members. They agree on the frequency of meetings, how often principal investigators or other key trial staff members attend meetings, and the ways in which members can communicate with research teams between meetings. They determine reimbursement policies, if appropriate, and mechanisms by which individuals or groups can raise concerns with research teams and with off-site trial sponsors in the event that a conflict or concern related to the site emerges. They determine the conditions under which members must respect confidentiality.

5. Research teams and relevant stakeholders determine what education is needed in order to enhance stakeholder understanding of, and engagement with, a specific planned trial and research more generally. They discuss together and agree on a stakeholder education plan to cover the life-cycle of the trial. It defines the range of stakeholders that could benefit from specific education about clinical trials and general research literacy. It outlines the level of knowledge that is optimal and desired by stakeholders to support effective engagement, depending on the type of engagement defined for each stakeholder. They identify the training needs of stakeholder advisory mechanism members and the activities that will build their capacity to understand concepts, purposes, practices, and limitations of clinical trials and increase their ability to provide meaningful input to the research process. The plan describes the methods and frequency of educational activities, the stakeholders who could also deliver or facilitate the delivery of these activities, and an indication of the frequency with which the plan will be reviewed and the criteria to be used to evaluate its success.
6. Research teams maintain clear written records of discussions and agreements with relevant stakeholders, including requests, concerns, recommendations, actions taken by the research team, and any unresolved issues that require follow-up. They document stakeholder education activities, including questions that arise, topics that cause confusion, and suggestions for future education activities.

4.3 Communications and issues management plan^k

4.3.A Definition and relevance to good participatory practice

The communications and issues management plan is developed prior to trial implementation to exclusively address external communication and is harmonised with the communication plans of national and local response coordination bodies. It includes strategies to create a supportive and conducive environment for trial initiation and implementation and to anticipate and effectively address issues that arise. It describes policies and strategies that will increase broad awareness of the trial; facilitate dissemination and understanding of correct information about trial design, conduct, and results; and coordinate communication between the research team and relevant stakeholders. It outlines how research teams intend to manage issues of concern or any unexpected developments that may emerge before, during, or after the trial, including those that could limit the support for, or success of, the specific trial or future trials. For example, the communications and issues management plan for a Phase 1 trial needs to anticipate and address fears that may be expressed at all levels in a society about the possibility that the trial may import the pathogen in question.

^kAdditional guidance: Communications Handbook for Clinical Trials: Strategies, tips, and tools to manage controversy, convey your message, and disseminate results(72).

The risk that unexpected developments will negatively affect a trial can be mitigated if research teams work closely with relevant stakeholders to identify and plan for such risks and if relevant stakeholders provide advice and direction on how to avert a crisis by resolving issues when they arise. The plan includes a crisis communication component with a clear chain of communication. Examples of the types of issues that may emerge include negative media coverage; rumours about the trial; socio-cultural taboos around certain trial procedures; developments in other emerging pathogen trials; premature closure of a trial for reasons of harm, futility, or proven efficacy in interim analyses; recruitment challenges; serious adverse events (including deaths); and protocol-related issues.

4.3.B Special considerations

Effective internal communication, especially across multidisciplinary teams, is a prerequisite to effective external communication. It is highly advantageous for research teams to participate regularly in communications networks of emerging pathogen trials to share and discuss issues and their potential management and lessons learned. Issues can include trial participant stigma, health care worker concerns, confidentiality, results dissemination issues, and strategies for addressing them. Furthermore, active research team participation in government-coordinated communication networks for the epidemic response enhances both the response and research conduct.

4.3.C Good participatory practice for communications and issues management planning

1. Research teams and relevant stakeholders comprehensively identify potential audiences within and surrounding the research area as well as regionally, nationally, and internationally. They identify and list all known issues that could emerge and undermine trial success before, during, or after trial completion. They discuss and develop a communications and issues management plan that supports open channels of communication throughout the trial's life-cycle. It describes diverse stakeholder information needs from early phases of stakeholder engagement to recruitment, enrolment, trial closure, and results dissemination. It includes agreement on the frequency of updates and mechanisms for urgent communication with politicians and Ministry of Health personnel who may be called upon to explain the trial publically at any time. It spells out procedures and timelines for disseminating information and procedures for promptly addressing inquiries about the trial or research in general. The plan includes designation of key media spokespersons and a social media coordinator who is responsible for active tracking, media analysis, and timely strategic messaging. It spells out the frequency with which the plan will be reviewed and the criteria by which to monitor and evaluate its success.
2. Research teams and relevant stakeholders determine the key messages to be communicated about the trial, such as the purpose, risks, benefits, ongoing progress, closure, and results dissemination, and the various communication methods that will be used for specific stakeholders, taking into account literacy levels and the need for understandable language and translation. Research teams develop these communication materials in collaboration with stakeholders. Together they determine trusted local stakeholders with integrity who could deliver or facilitate communications activities and any specific training that they may need to effectively deliver messages.
3. The site-level strategy to manage unexpected developments and emerging concerns designates key trial site staff who are responsible for addressing urgent issues and establishes the chain of communication for crisis management within the research team and with relevant stakeholders. It details the process for developing key messages, question and answer briefing notes, and other materials created to address concerns. It defines clear processes by which media reports and media requests will be handled. It identifies relevant stakeholders who can act as advisers and help implement issues management procedures.

4. Research teams implement the plan and maintain clear written records of discussions, agreements, communication activities, and all issues that emerge, how they are responded to, and their outcome. This includes relevant stakeholder recommendations, actions taken by the research team, and any unresolved issues that require further follow-up.

4.4 Protocol development

4.4.A Definition and relevance to good participatory practice

Protocol development is the process of creating and modifying a trial protocol so that it fully describes the rationale, objectives, design, methodology, statistical considerations, ethical considerations, and implementation of a trial. Formative research findings can usefully inform protocol development. Among stakeholders that can provide meaningful input into aspects of trial protocol development, community stakeholders bring valuable expertise to assist in ensuring that trial designs and protocol procedures are locally appropriate and acceptable to the trial population and optimize successful trial implementation.

4.4.B Special considerations

1. Opportunities vary by trial for protocol review and input by local research teams and relevant stakeholders. Although protocol development may be largely centralized in crisis situations or for multisite trials, it is good practice to incorporate mechanisms to facilitate stakeholder input into protocol development early in the process. Documenting and sharing community stakeholder input into protocol development with protocol review bodies is useful, even when not explicitly required by such bodies.

4.4.C Good participatory practice for protocol development

1. Trial sponsors provide opportunities and time for local research teams to engage actively in expedited trial protocol development. Local research teams provide opportunities and time for local stakeholders, in particular community stakeholders, to contribute to decisions about trial design issues and procedures, including the products to be tested, trial objectives, recruitment strategies, informed consent materials and procedures, reimbursement policies, counselling approaches, follow-up procedures, and post-trial access to trial products or procedures.
2. Research teams maintain clear and transparent communication about the protocol development process with formal stakeholder advisory mechanisms and provide regular updates about protocol review and approval processes to relevant stakeholders. They provide protocol summaries to relevant stakeholders and make technical information as accessible as possible by translating materials or facilitating workshops, as necessary. They make full, final protocols of trials available and easily accessible to stakeholders.
3. Research teams maintain clear written records of discussions and agreements. This includes relevant stakeholders' recommendations, actions taken by the research team, and any unresolved issues that require follow-up.

4.5 Informed consent process¹

4.5.A Definition and relevance to good participatory practice

Informed consent is a decision to participate in research, taken by a competent individual who has received the necessary information; who has adequately understood the information; and who, after considering the information, has arrived at a decision without having been subjected to coercion, undue influence or inducement, or intimidation. Informed consent is based on the principle that competent individuals are entitled to choose freely whether to participate in research. Informed consent protects the individual's freedom of choice and respects the individual's autonomy(74).

In the informed consent process, research staff members inform the prospective participant or his or her legal representative about the trial, including about the potential risks and benefits, trial procedures, and what is expected of the participant. When an individual provides consent, this is documented on the informed consent form. Informed consent is an ongoing process. Participants may decide to drop out of the trial at any point, without being subject to any penalty, even after providing consent to enrol in the trial. In emergency situations, children and adolescents without guardians can be assessed for their capacity to understand and competency to provide assent. A legal guardian can be designated to provide consent for an assenting child or adolescent to participate in a trial, subject to ethics approval.

A wide range of stakeholders can help research teams develop locally acceptable, effective informed consent procedures and materials. These may include special materials for families in situations where an individual needs familial approval before he or she can provide individual informed consent to trial participation. In some instances, individual informed consent cannot be obtained before community permission is sought, following assurances that there are no social or economic repercussions for participants or undue or unintended hardship imposed on households. In no circumstance, can a competent person participate in a trial without providing individual and freely given informed consent.

4.5.B Special considerations

Community stakeholders can provide research teams with invaluable advice to improve the informed consent process and materials. However, actual implementation of the informed consent process between an individual and the research staff is confidential and is conducted in accordance with *Good Clinical Practice*(67) and international ethics guidance(74) . Only designated research staff members have access to confidential information about trial participant identity.

4.5.C Good participatory practice for the informed consent process

1. Research teams discuss the following topics with community stakeholders during development of the informed consent materials and procedures:
 - a. Who needs to be consulted locally to enable research teams to invite individuals to join the trial.

¹Additional guidance: Informed consent is the cornerstone of ethically conducted research and is explicitly discussed in guidance documents that address the overall ethical conduct of research, such as the *Declaration of Helsinki*(73), *CIOMS guidelines*(74), *The Belmont Report*(66), *Good Clinical Practice*(67), the *World Health Organization Handbook for Good Clinical Research Practice*(68), the *Nuremberg Code*(76), the *Nuffield Council Guidance on health research in developing countries*(76),(77), *UNAIDS/WHO Ethical considerations in biomedical HIV prevention trials*(3), the *UNESCO Universal Declaration on Bioethics and Human Rights*(78), and relevant national guidelines. There are extensive literature and other resources on the development of informed consent processes in multiple contexts, including a range of innovative approaches to measure and assess participant understanding, to address literacy issues, and to accommodate the desire of participants to consult with families and friends(79)(80)(81)(82)(83).

- b. What local cultural practices may affect individual decision-making ability, and how working within these structures can be facilitated while ensuring protection of individual autonomy to provide informed consent or refusal to participate.
 - c. The general literacy level of the population to be recruited, how to assess the literacy level of prospective participants, and considerations and requirements for illiterate participants, including discussion of possibilities of who may serve appropriately as a witness to the informed consent process and how the informed consent of the individual will be documented.
 - d. The prevalence of different languages in the area and which languages are required for obtaining informed consent from individuals and permission from families and communities, where indicated.
 - e. Legal and local forms of identity (name and age) verification and local practices concerning the use of names.
 - f. Legal, local, and trial sponsor definitions of a 'minor' and consideration of legal and local determinations of who can serve as a minor's guardian, including how the question of trial participation of children and adolescents without guardians will be handled.
 - g. How situations in which there are doubts about someone's capacity to give their own consent will be addressed.
 - h. Locally appropriate reimbursement and/or compensation for travel and time.
 - i. Appropriate strategies to ensure participant rights are protected, including voluntariness of participation, confidentiality, avoidance of undue inducement, and mitigation of social desirability in influencing individual agreement to enrol.
 - j. Strategies to ensure comprehension of informed consent and critical trial-related terms and concepts, including the use of translated and piloted visual or audio materials, flipcharts, props, analogies, and other supportive materials and methods, including materials to assess participants' ongoing consent.
 - k. Techniques to assess comprehension of trial participation and prevent therapeutic misconception, and the frequency with which they are to be used.
 - l. Explanation of potential trial-related harms and how such harms will be addressed (see Section 4.7).
 - m. Strategies to ensure that follow-up of participants after missed visits respects agreements between the participant and research team about how to contact the participant.
 - n. Consideration of the length of informed consent forms, the estimated time required to complete the informed consent process, and ways to pilot the informed consent materials.
 - o. Preferred ways for participants to contact research teams and contact stakeholders independent from the research team to ask questions or express concerns about trial participation.
2. Research teams maintain clear written records of discussions and agreements. This includes community stakeholder recommendations, actions taken by the research team, and any unresolved issues that require follow-up.

4.6 Standard of prevention and care^m

^m Additional guidance: *Infection prevention and control of epidemic- and pandemic-prone acute respiratory infections in health care WHO guidelines. 2014(84); Ethical considerations in biomedical HIV prevention trials* (page 13, selected

4.6.A Definition and relevance to good participatory practice

Prevention

Best-proven standard of prevention refers to the package of comprehensive state-of-the-art information and tools provided or made available to participants in an emerging pathogen prevention trial. The locally available standard of prevention in an emergency setting may be lower than the best-proven global standard. Determining what level of prevention a trial will offer requires deliberation with relevant stakeholders, including both women and men, about how best to achieve the highest level possible and what ethical justifications are required to support a trial providing a higher standard or a lower one that is aligned with that available to others in the population. Helping trial participants reduce their risk of acquiring an emerging pathogen in a crisis situation is a key ethical obligation of research teams. Providing a standard of prevention package in trials conducted in remote and underserved locations is a challenge that must be addressed. The components of the prevention package will vary according to the emerging pathogen and, beyond information, education, and communication materials in local languages, should include, for example, gloves and other barriers to prevent exposure in the case of a blood borne pathogen, male and female condoms in the case of a sexually transmitted infection, and insect repellent and bed nets in the case of an insect vector-borne illness. Trial sponsors and research teams must work with relevant stakeholders in establishing the type, scope, and process by which participants are provided with, or referred to services to access, the full prevention package.

Care and treatment

Best-proven standard of care refers to the best known and most effective measures available to treat emerging pathogen disease and prevent mortality. Optimised clinical management may simply be intensified supportive care, such as adequate rehydration, electrolyte correction, empiric antimalarial and antibacterial therapies, analgesics, and anti-emetic drugs, in the case of Ebola Virus Disease (EVD). The locally available standard of care in an emergency setting may be lower than the best-proven global standard, if one is in fact proven for the new disease, but should be increased in the context of a trial. Standard of care refers not only to care and treatment provided in a therapeutic trial, but also to services made available to individuals who are identified as having the emerging pathogen during the screening process and to trial participants who acquire it during an emerging pathogen prevention trial. Trial sponsors and research teams are ethically obligated to ensure that participants who acquire an emerging pathogen during a prevention trial will receive appropriate clinical evaluation and adequate care and treatment.

Comprehensive ancillary care

Access to comprehensive care can provide benefits for participants, contribute to their welfare, and improve clinical trial outcomes. Discussing the range of ancillary services that can be made available to participants at the trial site or via referral will assist relevant stakeholders in clearly understanding the breadth of services available and reasons for their inclusion or exclusion. Comprehensive care in a vaccine trial includes preventive, psychosocial, psychological, and clinical components of care, as well as health and social care services not directly related to the emerging pathogen itself or trial-related harm. Depending on the trial population and local health priorities, these include provision of female or male sexual and reproductive health care, management of other infectious diseases, nutrition and nutritional health, counselling, psychiatric care, and psychosocial services. It may not

circumstances in which biomedical HIV prevention trials should not be conducted and Guidance Point 13, page 45, Standard of HIV Prevention)(3); *The challenge of defining standards of prevention in HIV prevention trials*(85); and *The Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*(73); and WHO Guidance on ethics of tuberculosis prevention, care and control(86).

be possible to offer adequate ancillary care, depending on the surge capacity of the crisis response in addressing the needs of those already ill and at risk of serious sequelae and death.

How trial sites help participants to prevent acquisition of an emerging pathogen and provide access to care and treatment is often at the forefront of community stakeholder concerns. Successful deliberation with relevant stakeholders about trial participant prevention packages and provisions for their access to care and treatment is an integral part of the research and will have a significant influence on community stakeholder perceptions of an emerging pathogen trial.

4.6.B Special considerations

1. Deviations from expected standard of prevention packages at a trial site or among trial sites in multisite studies may be caused by national legal restrictions, immediate logistical constraints, or funding body restrictions. The possibility of a legal exemption for the trial can be sought. Effective discussions with implementing partners can result in the alleviation of logistical constraints so that an adequate prevention package is offered to all trial participants. Alternative funding streams or linkages with non-governmental or community-based organisations can assist research teams in finding ways to meet their responsibility to provide prevention methods and tools.
2. Research teams need to review the prevention package regularly, taking into consideration new information, improved education models, and novel risk reduction methods that have shown promise in other prevention trials for the same pathogen.
3. To improve relevant stakeholder understanding of the prevention package offered and the clinical trial process, research teams can describe a classical randomised controlled trial as comparing the experimental product plus an effective prevention package with the placebo (or comparator arm) plus the effective prevention package. An example of a method to increase understanding and acceptance of a randomised trial design is public randomisation ceremonies involving community stakeholders(87).
4. Just as care and treatment guidelines for an emerging pathogen may vary by country and from site to site in a multi-country trial, non-emerging pathogen-related care packages may vary, depending on local health priorities and local standards of care. Furthermore, treatment options may improve over time and research teams may need to modify their care and treatment plans as scientific knowledge accumulates and is validated by national and international authorities. Documenting these differences and any changes during trial conduct is important to eventual data analysis and interpretation of trial findings.
5. Stakeholders can advocate for access to experimental therapies through expanded access programmes(88) and this may be achieved if ethical and regulatory criteria are fulfilled.

4.6 C Good participatory practice for standard of prevention and care

1. Research teams and relevant stakeholders discuss and determine the trial's prevention package during the protocol development phase of a prevention trial and monitor for new information to help strengthen the prevention package.
2. Research teams determine which stakeholders already provide public health prevention services, what types of services they provide, and their capacity to provide adequate services, in order to plan for optimal referrals, linkages when necessary, and incorporation of prevention strategies for all arms of an emerging pathogen prevention trial.
3. Research teams and relevant stakeholders, including local public health authorities, discuss and agree on the comprehensive prevention package for the trial, taking into account the prevention package ethically required as adequate (a minimum) for the emerging pathogen trial protocol.

They consider current prevention standards and services available nationally and locally, current national laws on emerging pathogen prevention strategies and services, national ethical guidance on research, and the trial's funding source. They address how participants can be offered a comprehensive package, through the trial or through referral mechanisms. They define the prevention services to be made available and accessible to partners and families of trial participants, should the trial participant become infected. They pay careful attention to the impact that services offered by the trial, as well as those to which participants will be referred by the trial, could have on local prevention services in a crisis setting.

4. During protocol development, research teams and relevant stakeholders discuss and agree on the standard of care and treatment for individuals who are identified during the screening process as having acquired the emerging pathogen already and for individuals who acquire the pathogen during the trial. They discuss clinical management of women who are identified as pregnant during the screening process or who become pregnant during the trial. They determine whether any emerging pathogen or non-emerging pathogen-related services will be available to the partners and families of trial participants.
5. Research teams identify local care and treatment services, local non-governmental or community-based organisations, and survivor support groups; determine their capacities; and seek their views and perspectives in order to design optimal referral mechanisms. They identify the existence and capacity of local social care and primary health-care services and of secondary and tertiary diagnostic and treatment services to enable the provision of appropriate referrals for non-emerging pathogen illnesses, should the need arise.
- 6.. Research teams and relevant stakeholders discuss the care and treatment package, taking account of the trial protocol ethical (minimum) requirements, current national and international care and treatment guidelines and policies, and local provision of care and treatment services. They anticipate the numbers of people who may require immediate treatment because they will be found to have been infected already during screening or because they are likely to acquire the emerging pathogen during a prevention trial. They agree on the care and treatment services that will be offered on site and whether trial participants will have priority access to services offered through referral mechanisms. They discuss any additional emerging pathogen care and non-emerging pathogen care that that community stakeholders recommend the trial site offer to participants and whether these services are feasible.
7. Research teams and relevant stakeholders, including health authorities, discuss local health institution responsibilities and proposed trial sponsor and implementer commitments regarding who will finance and who will deliver specific care and treatment services, as well as the duration of care and treatment services being provided by each partnering stakeholder. They assess the impact that any services offered by the trial, or to which participants will be referred, could have on local services and the need for strengthening sub-standard health facilities and laboratories to ensure basic standard of care. They discuss improvements to care and treatment services for health care delivery in trial locations, as well as at trial sites. They consider how to gather and analyse information on the numbers of people acquiring the emerging pathogen during the trial who are successfully referred for standard of care, barriers to accessing care and treatment programmes, and other issues that may arise.
8. Research teams and relevant stakeholders discuss rights to and mechanisms for optimal referral procedures and the most appropriate way to ensure that all individuals screened and enrolled are aware of these rights and how to access care and treatment services. Research teams include a description of the care and treatment package in informed consent forms for screening and trial enrolment.
9. Research teams inform research ethics committees and seek approval for any deviations from the reviewed protocol concerning standard of prevention and care. They maintain clear written

records of discussions and agreements about standard of prevention and standard of care. This includes relevant stakeholder recommendations; actions taken by the research team; aspects of prevention, care, and treatment that will not be offered and why; and any unresolved issues that require follow-up. They determine with relevant stakeholders how agreed standard of prevention and care will be implemented and monitored, including uptake and standards of referral services.

4.7 Policies on trial-related harmsⁿ

4.7.A Definition and relevance to good participatory practice

Policies on trial-related harms describe how research teams will document physical, psychological, financial, or social harms that are determined to be associated with trial participation and whether and how such harms will be addressed and mitigated. A key ethical obligation of research teams is to maximize benefits and minimize harms for trial participants. Relevant stakeholders can provide valuable input about possible social harms of trial participation, paying particular attention to individuals or groups who may be vulnerable, marginalised, stigmatized, or who have less power in society. They can advise on local expectations about research team obligations to address trial-related harms. Clearly explaining how trial-related harms will be handled and mitigated, in discussions with stakeholders before a trial starts, can significantly influence community stakeholder perceptions of a trial and how well it addresses concerns.

4.7.B Special considerations

Sponsors typically give specific and binding guidance to research teams on how to determine and report physical harms as adverse events. It is good practice to define similarly stringent procedures for the determination, documentation, reporting, and management of other harms that trial participants may experience. Social and psychological harms due to trial participation include stigma and discrimination; verbal, emotional, physical, or sexual abuse; limited mobility due to isolation; potential future problems obtaining health insurance; possible travel bans; and concerns about disclosure to sexual partners.

4.7.C Good participatory practice for policies on trial-related harms

1. Research teams and relevant stakeholders discuss anticipated harms that might occur due to trial participation and develop policies on trial-related harms. They consider strategies to prevent or reduce the risk of trial-related harms, measures to encourage and facilitate their reporting, and methods to investigate events that have been reported indirectly, such as through a third party, taking confidentiality issues into account. They determine procedures for reporting harms and whether these will be reported to sponsors, ethics committees, and regulatory bodies, even if not specifically required by them. They agree on procedures for ensuring optimal referrals to appropriate services for trial-related harms. They develop strategies to inform trial participants of the potential social and other risks of engaging directly with journalists.
2. Research teams and relevant stakeholders discuss compensation or insurance policies, when applicable, for specific trial-related harms, coverage provided by the policies, how claims are made, and how participants are informed of their rights in relation to the policies.
3. Research teams and relevant stakeholders review follow-up strategies to reduce trial-related harms over the course of the trial.
4. Research teams maintain clear written records of discussions and agreements. This includes

ⁿ Additional guidance: *International Ethical Guidelines for Biomedical Research Involving Human Subjects*(74) (Guideline 19, page 78 right of injured subjects to treatment and compensation).

recommendations, actions taken by the research team, and any unresolved issues that require follow-up.

4.8 Trial accrual, follow-up, and exit

4.8.A Definition and relevance to good participatory practice

Trial accrual, follow-up, and exit activities include the recruitment, screening, enrolment, follow-up, and exit of trial participants in emerging pathogen prevention and treatment trials. Community stakeholders can provide pertinent information on how to design socially and culturally acceptable strategies for recruitment, screening, enrolment, follow-up, and exit. Including them in the process of developing these strategies allows them to play an important role in identifying and mitigating trial-related stigma, misconceptions, and miscommunication.

4.8.B Special considerations

1. Whereas participants in a therapeutic trial may be more likely to be hospitalised with continuity of care assured, participants in a prevention trial who miss visits must be followed up in a way that respects agreements between the participant and research team about how to contact the participant.
2. Exiting a trial may present changes in what participants may have become accustomed to with regard to clinical care and the impact of the trial on their social relationships. Anticipation and discussion of these issues between research teams and community stakeholders will help in the development of appropriate strategies to support participants upon trial exit.

4.8.C Good participatory practice for trial accrual, follow-up and exit

1. Research teams discuss with relevant stakeholders the trial accrual, follow-up, and exit processes, taking into account strategies and messages that are socially and culturally appropriate, that meet the needs of specific stakeholders in terms of language and literacy, and that draw on a range of communication modes, including written, oral, and visual. They discuss procedures to anticipate, monitor, and mitigate trial-related stigma resulting from ineligibility to enrol or from enrolment itself.
2. Research teams establish procedures for training and supervising trial site staff about creating respectful relationships with participants and fostering an environment that is non-judgmental and welcoming. They establish strategies to ensure the confidentiality of participants during trial visits and while following-up participants outside the trial clinic and after trial exit. They adopt procedures for informing participants about trial results and trial product assignment, when available. They determine procedures for transfer of care at the end of follow-up or trial closure, such as providing participants with referrals to ongoing care, supportive services, survivor groups, and cohort studies.
3. Research teams provide relevant stakeholders with high-level summary updates on trial accrual, follow-up, and trial exit processes at agreed intervals. They do not release individual identifying data and they protect the confidentiality and security of trial participants at all times. They seek advice from relevant stakeholders on how to improve accrual, follow-up and exit processes, and messages. They maintain clear written records of discussions and agreements, including ongoing discussions about ways to modify strategies.

4.9 Trial closure, results dissemination, and post-trial access to trial products or procedures^o

^oAdditional guidance: *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries* (Recommendation 4.1)(89)

4.9.A Definition and relevance to good participatory practice

Trial closure occurs when all participants have exited from the trial and all trial procedures are completed. Results dissemination involves dissemination of trial results to participants, community stakeholders, and the public at large, as well as the unblinding of participants to trial group or arm assignment. Effectively engaging relevant stakeholders about trial closure and results dissemination in a transparent manner builds trust and lays a positive foundation for future research. In the event that a trial is stopped early or unexpectedly, timely research team-initiated dialogue with relevant stakeholders will minimize the risk of misinformation.

The term 'post-trial access to trial products or procedures' refers to making the product or procedure tested in the trial, whether a vaccine, prevention method, or treatment, available to trial participants and local community stakeholders (1) should the new product or procedure be scientifically validated or approved by relevant authorities or (2) in the form of follow-on, open label, or other such studies before product licensure or approval, should an efficacy or effectiveness trial have a compelling positive finding, with no safety concerns. Benefits to stakeholders who participate in research should be maximised, with post-trial access provisions clearly spelled out in trial protocols. How trial sites communicate and interact with community stakeholders about issues of access to the prevention product, procedure, or therapy studied is likely to have a significant influence on their perceptions of a trial.

4.9.B Special considerations

1. Trials may run to completion per protocol or may be stopped early for scientific reasons or due to unforeseen circumstances. In multicountry, multisite, stepped-wedge, and other trials, sites may complete participant follow-up at different times. Thus, while some sites might be closed for participant follow-up, research teams at other locations may continue to see participants.
2. Ownership of data, issues of publication, and release of trial results vary by trial and may be strictly delineated in non-negotiable terms by sponsors or product manufacturers. Where trial product manufacturers are publicly traded companies, there may be legal requirements that affect the timing and methods for public announcement of a trial closure.
3. Post-trial procedures are required to continue the identification and reporting of adverse events, particularly in trials stopped due to evidence of harm. This may involve transition of responsibility for monitoring from the study team to the national health care system.
4. In principle, trial participants and local community stakeholders should be among the first to gain access to the new prevention or treatment products, should they be found to be safe and effective. Availability of newly-proven prevention or treatment products or procedures for trial participants and other community stakeholders will depend on several factors. After a trial is completed, other trials may be needed to corroborate findings. After results from relevant trials are available, it may take time for normative agencies and appropriate regulatory authorities, including national governments, to approve the new product or procedure. National regulatory authorities make the ultimate decision about whether a new product or procedure will be approved for use within a particular country. Approval processes and timelines will differ by product or procedure and by country, which can influence local post-trial access. Availability and pricing of new products or procedures may be affected by product-manufacturer parameters as well as by agreements with trial sponsors. However, if the product or procedure has been proven efficacious, post-trial access may be granted through open-label or compassionate use.

4.9.C **Good participatory practice for trial closure, results dissemination, and post-trial access to trial products or procedures**

1. Research teams discuss possible trial closure scenarios with relevant stakeholders early in the research life-cycle. These include trial closure as scheduled per protocol; early closure due to

evidence of harm, futility, or clear protective benefit in interim analyses of trial data; early closure because of evidence of harm or of clear protective benefit from a different trial evaluating the same product; or early closure due to unforeseen circumstances, such as administrative or financial reasons, stakeholder objection, or sudden social unrest.

2. Research teams consult with relevant stakeholders to develop a results dissemination plan, detailing strategies to manage expectations about trial results, including by preparing participants and relevant stakeholders for all possible outcomes; planned timelines for trial closure at the site and at other sites, completion of data analyses, and availability of results; procedures and timelines for those who will be informed of trial results in confidence prior to public release; and plans for public dissemination. They ensure that trial participants are provided opportunities to learn trial results before they are announced publicly.
3. Research teams consult with relevant stakeholders to develop and pilot key messages and to determine how the messages will be finalised when the results are known and what communication methods will be used. The messages will explain implications of the results for the area where the trial was conducted, limitations of the trial, and its ability to generalise findings for specific aspects, such as by sex, age, behaviour, or location.
4. Research teams consult with relevant stakeholders about how best to disseminate trial results that may be of a sensitive nature or that may put certain individuals or groups at risk of harm or stigmatization. They discuss how and when participants will be informed of their trial group assignment and the procedures for contacting and informing trial participants of research results before they are announced publicly. They agree on whether and how to disseminate additional findings that are not related to the primary trial question but may be of interest to some stakeholders, such as reported behaviours concerning funeral practices for a blood borne pathogen, patterns of sexual networks for a pathogen that can be spread sexually, prevalence of other infections, or demographic data.
5. Research teams and relevant stakeholders discuss issues of data ownership, data access, and scientific publication, including how the research team will facilitate community stakeholder access to published trial results. They determine together how community stakeholder responses to the results will be systematically collected and documented. When publishing or sharing research in a scientific forum, it is important that community stakeholder interpretations be noted, particularly if they differ from the predominant scientific analysis. Research teams maintain clear written records of discussions regarding trial closure and dissemination messages, as well as documentation of responses to the results.
6. Research teams discuss with relevant stakeholders, early in the trial process, issues affecting future product or procedure availability, including the need for corroborated biomedical evidence, pursuit of licensure, production rights, additional marketing and distribution research, and post-trial monitoring provisions. They inform community stakeholders of their rights, the access plan, and the factors that could postpone or prevent their gaining access to the new prevention or treatment product or diagnostic procedure, such as the need to secure regulatory approvals or parameters related to the product manufacturer. They update community stakeholders as information becomes available.
7. Trial sponsors and research teams discuss and agree with national governments on responsibilities and funding for licensure requirements and access issues, should the prevention or treatment product or procedure under investigation be shown to be safe and effective. They discuss with relevant stakeholders, early in the trial life-cycle, expectations about and provisions for possible pre-licensure access, plans for follow-on, open label, cohort studies, or other studies, and how such pre-licensure access will be funded, in the event that a compelling positive result, with no safety concerns, is observed. They develop a clear strategy and funding mechanisms for how a prevention or treatment product or diagnostic procedure will be made

available and accessible to participants (at a minimum) rapidly, affordably, and sustainably, should it be shown to be safe and effective. They collaborate with multiple stakeholders, such as UN organisations, development partners, local governments, and non-governmental organisations to design and support the overall access strategy.

DECEMBER 2016

Appendix 1: Acronyms

AE – Adverse event
CAB – Community Advisory Board
CAG – Community Advisory Group
CBO – Community-Based Organisation
CIOMS – Council for International Organizations of Medical Science
EC – Ethics committee
DSMB – Data safety monitoring board
DSMC – Data safety monitoring committee
GCLP – Good Clinical Laboratory Practice
GCP – Good Clinical Practice
GMP – Good Manufacturing Practice
GPP – Good Participatory Practice
HIV – Human Immunodeficiency Virus
IDMC – Independent data monitoring committee
IRB – Institutional review board
NGO – Non-governmental organisation
REC – Research ethics committee
SOP – Standard operating procedure
UNAIDS – The Joint United Nations Programme on HIV/AIDS
WHO – World Health Organization

Appendix 2. Glossary

Accrual. The process of recruiting participants into a clinical trial in order to reach target participant numbers.

Activist. A person or group who acts on the behalf of a cause in order to bring about change.

Adverse event (AE). An unwanted effect experienced by a participant in a clinical trial. This may or may not be related to the product or procedure being studied.

Advocate. A person or group who acts on the behalf of individuals, groups, or a specific cause.

AVAC. An international, non-profit organisation that uses education, policy analysis, advocacy, and community mobilization to accelerate the ethical development and eventual global delivery of AIDS vaccines and other new HIV prevention options as part of a comprehensive response to the pandemic.

Blinded trial or masked trial. A clinical trial designed to prevent the participants, research teams, or both from knowing which participants are in the experimental arm or group and which are in the control arm or group of a trial, in order to reduce bias.

Clinical trial. A research study that uses human volunteers to answer specific questions about the safety, efficacy or effectiveness, and medical effects of a specific procedure, medication, product, or treatment. A clinical trial process may include Phases I, II, IIb, III, and IV (post-marketing evaluation).

Community advisory boards (CABs) or community advisory groups (CAGs). Boards or groups composed of individuals or stakeholder representatives that act as an independent advisory voice and facilitate community stakeholder participation and involvement in the research process. They meet regularly with research team representatives, inform community stakeholders about proposed and ongoing research, and provide feedback to research teams about local norms and beliefs, as well as local views and concerns that arise in specific trials.

Community groups. Groups of individuals who come together to act on behalf of common interests, goals, and values but whose organisation does not require formal designation or registration.

Community stakeholders. Individuals and groups who are ultimately representing the interests of people who would be recruited to or participate in a clinical trial, and others locally affected by a trial. Examples of 'community stakeholders' are the population to be recruited, trial participants, people living in the area where the research is conducted, survivors of the emerging pathogen and their families, local survivor groups or networks, people in the area affected by the emerging pathogen epidemic, local non-governmental organisations, community groups, and community-based organisations. (See **stakeholders**.)

Condom. A sheath or pouch that is worn either over the penis (male condom) or inside the vagina (female condom) during sexual intercourse, for the purpose of protecting against sexually transmitted infections (including HIV) or preventing pregnancy. (See **female condom** or **male condom**.)

Confidentiality. The principle that protects the rights of trial participants regarding prevention of unauthorized disclosure of personal information to third parties during data collection, storage, transfer, and use.

Control arm or group. The group of participants in a clinical trial who receive the placebo or control product or procedure. (See **placebo**.)

Data and safety monitoring board (DSMB) or independent data monitoring committee (IDMC). An independent committee established by a trial sponsor to assess, at intervals, the progress of a clinical trial, safety data, and critical efficacy or effectiveness endpoints. A data and safety monitoring board may recommend to the sponsor that a trial be stopped or modified if there are safety concerns, if trial objectives have been achieved, or if assessment of trial progress reveals that continuing the trial would be futile since it will no longer be possible to answer the research question that the trial is addressing.

Ethics committee. See **research ethics committee**.

Experimental arm or group. The group of participants in a clinical trial that receives the procedure, product, or drug being studied.

Female condom. A strong, soft pouch that when inserted in the vagina before vaginal intercourse, provides protection against pregnancy and most sexually transmitted infections, including HIV. During anal sex, the female condom, when placed on the penis after removing the inner ring, provides protection against most sexually transmitted infections, including HIV. Currently made of polyurethane or a synthetic latex, the female condom is stronger than the natural latex used in male condoms, odourless, non-allergenic, and usable with oil-based and water-based lubricants. For vaginal intercourse, it can be inserted vaginally prior to intercourse, is not dependent on male erection, and does not require immediate withdrawal after ejaculation. (See also male condom.)]

Formative research activities. Activities that enable research teams to gain an informed understanding of local populations, socio-cultural norms and practices, local power dynamics, local perceptions, channels of communication and decision-making, and local history of research, as well as the needs and priorities of people locally affected by or able to influence a clinical trial. Formative research activities usually constitute the initial phase of stakeholder outreach and engagement.

Futility. The inability of a clinical trial to achieve its objectives. This determination may be suggested, for example, during a confidential interim analysis of trial data by a data safety monitoring board.

Good Clinical Laboratory Practice (GCLP). Guidelines that set a standard for compliance by laboratories involved in the analysis of samples from clinical trials. These guidelines provide guidance to ensure that trial laboratory data are reliable, repeatable, auditable, and easily reconstructed in a research setting.

Good Clinical Practice (GCP). Internationally recognized guidelines for designing, conducting, recording, and reporting clinical trials in which humans participate. GCP provides guidance to ensure that trial data are credible and to protect the rights, safety, and well-being of trial participants. The guidelines were issued by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use.

Good Manufacturing Practice (GMP). Good manufacturing practices are quality assurance practices that ensure that products are consistently produced and controlled to the quality standards appropriate to their intended use and as required by the marketing authorization. Good manufacturing practices are aimed primarily at diminishing the risks inherent in the production of any pharmaceutical or medical device.

Good Participatory Practice for Emerging Pathogens (GPP-EP). Good participatory practice (GPP) guidelines provide trial sponsors and implementers with systematic guidance on how to effectively engage with stakeholders in the design and conduct of prevention and treatment trials for emerging and re-emerging pathogens that are likely to cause severe outbreaks in the near future, and for which few or no medical countermeasures exist.

Human immunodeficiency virus (HIV). The virus (retrovirus) that weakens the immune system, ultimately leading to acquired immunodeficiency syndrome (AIDS).

Implementer. See **trial implementer**.

Informed consent. A process by which a competent individual voluntarily confirms his or her willingness to participate in a particular clinical trial after having been informed of all aspects of the trial that are relevant to the individual's decision to participate. In cultural contexts in which a person's health is considered a family asset, familial approval may be required before an individual can consent to participate in a trial. Informed consent is an ongoing process throughout the course of a clinical trial.

Institutional review board (IRB). See **research ethics committee**.

Male condom. A sheath designed to be worn over the penis during vaginal, anal, or oral intercourse as a means of preventing sexually transmitted infections, including HIV, or preventing pregnancy in the case of vaginal intercourse. (See also **female condom**.)

Network or research network. A cooperative of research institutions or centres conducting clinical trials under a common research agenda.

Non-governmental organisation (NGO). A not-for-profit, registered entity or group that is organised at the local, national, or international level but that is not an agency of local or national governments.

Placebo. An inactive substance that is designed to appear like an experimental product being studied in all aspects except for the absence of the active ingredient under study. In controlled clinical trials, the safety and effectiveness of an experimental product can be assessed by comparing data from the experimental product trial arm to those from the placebo arm.

Product or trial arm assignment. The specific study product or procedure, such as the experimental or 'active' arm or the placebo arm, to which a participant is assigned for the designated follow-up period. (See **placebo** and **experimental arm**.)

Protocol. A document that details the rationale, goals, design, methodology, statistical considerations, and organisation of a study or clinical trial. A protocol describes a scientific study designed to answer specific research questions and describes how the health and rights of the trial participants will be safeguarded.

Randomisation. A method based on chance alone by which trial participants are assigned to a trial arm or group. Randomisation ensures that the only intended difference between trial arms or groups is which product or procedure a trial participant is exposed to during the trial.

Randomised trial. A clinical trial in which participants are assigned by chance to one of the trial arms or groups. (See **randomisation**.)

Regulatory authorities. Government agencies charged with carrying out the intent of legislation that constrains the actions of private individuals, businesses, organisations, institutions, or government bodies. In most countries, one or more regulatory agency may be responsible for ensuring the safety and effectiveness of health products and the correct conduct of clinical trials.

Research ethics committee (REC) or institutional review board (IRB). An independent body made up of medical, scientific, and non-scientific members whose responsibility is to protect the rights, safety, and well-being of human participants involved in a clinical trial. Research ethics committees review and approve the initial protocol, review materials to be used in recruiting and consenting trial participants, and provide continuing review of a trial protocol and any amendments. The term 'institutional review board' is common in the United States of America, whereas other countries commonly use the term 'research ethics committee' or 'independent ethics committee'.

Research network. See **network**.

Research team. A group of investigators and staff involved in implementing a prevention or treatment trial or in studying diagnostic, epidemiological, clinical, anthropological, human behaviour, or other aspects of an emerging pathogen. Research teams can include investigators and staff at a specific trial site as well as investigators and staff working at coordinating centres, institutions, or agencies.

Scientific process. A recognized systematic way to form and test hypotheses by designing controlled experiments to collect data, analyse results, and draw conclusions, in order to acquire new knowledge or to correct, refine, and integrate previous knowledge.

Seroconversion. The process by which a newly infected person develops antibodies that can be detected by an antibody test. Development of antibodies may occur anywhere from days to weeks following infection with an emerging pathogen.

Sexually transmitted infections (STIs). Infections caused by microorganisms that are transmitted from one person to another during sexual or intimate contact.

Stakeholders or trial stakeholders. Individuals, groups, organisations, governments, or other entities that are affected by the outcome of an emerging pathogen prevention or treatment trial or that can influence proposed research through their input and actions. (See **community stakeholders**.)

Standard operating procedure (SOP). A document that gives step-by-step instructions for how to conduct a procedure, in order to ensure that each staff member can perform the procedure in the same way.

Stigma. Stigma refers to a pattern of prejudice, discounting, discrediting, and discrimination directed at people perceived to have been infected or affected by an emerging pathogen, their significant others and close associates, and their social groups and communities.

Trial arm or group. A group within a clinical trial formed of participants who have been assigned a particular product or procedure during a trial. (See **control arm or group**, **experimental arm or group**.)

Trial implementer. Investigators, research staff, and all others specifically responsible for executing prevention and treatment trials for emerging pathogens. Implementers may be employed by governments, government-sponsored networks, non-governmental organisations, academic institutions, the pharmaceutical industry or other companies, foundations, or public-private partnerships.

Trial life-cycle. The entire process of a trial, starting from developing the initial concept and writing the protocol and continuing through to the implementation and conduct of the trial to completion, exiting of participants, dissemination and reporting of results, and post-trial access.

Trial participant (or trial volunteer). A competent individual who voluntarily provides informed consent to participate in a clinical trial. Trial participants are assigned to a particular trial arm or group in which they receive a particular product or procedure assignment. Trials may involve a non-competent participant only if consent to his or her participation has been legally and ethically provided.

Trial sponsor. An entity that is responsible for initiating, managing, or financing a trial but not for conducting a trial. The sponsor may be a pharmaceutical company, governmental agency, academic institution, non-governmental organisation, or private or other organisation.

UNAIDS (Joint United Nations Programme on HIV/AIDS). A joint venture of 10 UN organisations in the AIDS response to help prevent new HIV infections, care for people living with HIV, and mitigate the impact of the epidemic. UNAIDS is the main advocate for accelerated, comprehensive, and coordinated global action on the HIV epidemic.

Unblinding or unmasking. The process of revealing trial participants' product or procedure assignments. Unblinding involves informing participants about which product they were assigned to during the trial.

Vaccine. A compound that stimulates the body's immune response in order to prevent or control an infection. A vaccine is typically made up of parts of a bacterium or virus and cannot itself cause an infection.

World Health Organization (need the approved definition)

Appendix 3. Additional guidance

The Belmont Report, 1979

This report was written by the US National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research, which was established after the US public learned about the Tuskegee Syphilis Study. The Belmont Report established the foundational ethical principles of respect for persons, beneficence, and justice for research involving human volunteers.

Citation: National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report: Ethical Principles and Guidelines for the protection of human subjects of research*. Washington, DC, Department of Health, Education, and Welfare, 1979.

Universal Declaration on Bioethics and Human Rights, 2005

This Declaration anchors the fundamental principles of bioethics in the rules that govern respect for human dignity, human rights, and fundamental freedoms, ensuring respect for the life of human beings and enshrining bioethics in international human rights. It promotes equitable access to medical, scientific and technological developments through rapid knowledge dissemination and the sharing of benefits, with particular attention to the needs of low- and middle-income countries.

Citation: United Nations Educational, Scientific, and Cultural Organisation (UNESCO). Universal Declaration on Bioethics and Human Rights, 2005.

Declaration of Helsinki, 1964(73)

This declaration of the World Medical Association is often considered to be the first document to set world standards for research involving human volunteers.

Citation: World Medical Association. *World Medical Association Declaration of Helsinki: Ethical Principles for Medical Research Involving Human Subjects*. Helsinki, World Medical Association General Assembly, 1964; latest amendment at the 59th WMA General Assembly, Seoul, 2008.

Ethical considerations in biomedical HIV prevention trials, 2007

This is an ethical guidance document, issued by UNAIDS and WHO, for biomedical HIV prevention research. This document is a revision of *Ethical considerations in HIV preventive vaccine research*. UNAIDS guidance document. Geneva, UNAIDS, World Health Organization, 2000.

Citation: *Ethical considerations in biomedical HIV prevention trials*. UNAIDS guidance document. Geneva, UNAIDS, World Health Organization, 2007 (*additional guidance point added in 2012*).

Guideline for Good Clinical Practice, 1996

This guidance document was issued by the International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use and outlines an international ethical and scientific quality standard for designing, conducting, recording and reporting trials that involve human volunteers.

Citation: *Guideline for Good Clinical Practice*. ICH harmonised tripartite guideline. Geneva, International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, 2006.

International Ethical Guidelines for Biomedical Research Involving Human Subjects, 1993

These guidelines were published by the Council for International Organizations of Medical Science (CIOMS) and added guidance around conducting research in developing countries to the body of ethical guidelines. The 2002 version supersedes the 1982 and 1993 guidelines.

Citation: *International Ethical Guidelines for Biomedical Research Involving Human Subjects*. Geneva, Council for International Organizations of Medical Sciences, 2002.

Nuffield Council on Bioethics, 2002

The 2002 Nuffield Council on Bioethics report on the ethics of research related to healthcare in developing countries provided an ethical framework for designing or conducting externally sponsored research in the developing world. The 2004 follow-up report, co-hosted with the Medical Research Council of South Africa, discussed how the guidelines could be applied in practice, particularly in light of conflicting ethical advice.

Citation: *The ethics of research related to healthcare in developing countries*. London, Nuffield Council on Bioethics, 2002, and *The ethics of healthcare related research in developing countries: a follow-up discussion paper*. London, Nuffield Council on Bioethics, 2005.

Nuremberg Code, 1949

This code of research ethics came out of the ruling of the International Military Tribunal at the end of the Second World War, which prosecuted Nazi war criminals.

Citation: *Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10*. Washington, DC, US Government Printing Office, 1949.

Other references

Communications Handbook for Clinical Trials: Strategies, tips, and tools to manage controversy, convey your message, and disseminate results, 2010

The *Communications Handbook for Clinical Trials* is a practical guide developed for site-level research teams, communicators, advocates and others working on HIV prevention trials in developing countries. It provides guidance on how to anticipate and respond to the special communications challenges posed by the conduct of clinical research.

Citation: Robinson ET et al. *Communications Handbook for Clinical Trials: Strategies, tips, and tools to manage controversy, convey your message, and disseminate results*. Microbicides Media Communications Initiative and FHI, 2010.

Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries, 2001

A report and set of recommendations of the US National Bioethics Advisory Commission for US policy regarding conducting clinical trials in developing countries.

Citation: US National Bioethics Advisory Commission. *Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Volume I: Report and Recommendations of the National Bioethics Advisory Commission*, 2001.

Recommendation for Community Involvement in National Institute of Allergy and Infectious Diseases, HIV/AIDS Clinical Trials Research, 2009

The National Institute of Allergy and Infectious Diseases (NIAID) Division of AIDS (DAIDS) and Community Partners developed these recommendations as a tool for research teams and

community representatives to further expand and deepen community involvement in HIV/AIDS clinical trials research.

Citation: *Recommendation for Community Involvement in National Institute of Allergy and Infectious Diseases, HIV/AIDS Clinical Trials Research* (2009). Community Recommendations Working Group of Community Partners, a global group of community representatives affiliated with the National Institute of Allergy and Infectious Diseases (NIAID) HIV/AIDS clinical trials networks.

Ethical guidance for managing infectious disease outbreaks. World Health Organization, 2016.

The World Health Organisation developed this guidance as part of its response to emerging and re-emerging pathogens.

Citation: Guidance for managing ethical issues in infectious disease outbreaks. World Health Organization, 2016. ISBN 978 92 4 154983 7.

Guidance on ethics of tuberculosis prevention, care and control

The World Health Organisation developed this guidance for the response to tuberculosis.

Citation: World Health Organization. Guidance on ethics of tuberculosis prevention, care and control [Internet]. Geneva, Switzerland: World Health Organization; 2010 [cited 2016 Jun 22]. Available from: http://whqlibdoc.who.int/publications/2010/9789241500531_eng.pdf

Members of the International Working Group on GPP-EPP

Fred Binka MBChB, PhD, University of Health and Allied Sciences, Ho, Ghana

Patricia E. Fast MD, PhD, International AIDS Vaccine Initiative, New York City, New York and Stanford University School of Medicine, California, USA

Morenike Oluwatoyin Folayan BChD, FWACS, MBA, New HIV Vaccine and Microbicide Advocacy Society and Obafemi Awolowo University, Ile-Ife, Nigeria

Dirceu B. Greco MD, PhD, School of Medicine, Federal University of Minas Gerais, Belo Horizonte, Brazil

Stacey Hannah, MHS, AVAC, New York City, New York, USA

Elizabeth S. Higgs MD, MIA, DTMH, National Institute of Allergy and Infectious Diseases, National Institutes of Health, Bethesda, Maryland, USA

Shelley Lees PhD, MRes, BSc, RN, London School of Hygiene and Tropical Medicine, London, United Kingdom

Prince Bahati Ngongo BA, MSc, MBA, International AIDS Vaccine Initiative, Nairobi, Kenya

Cheikh Ibrahima Niang PhD, Université Cheikh Anta Diop, Dakar, Senegal

Vinh-Kim Nguyen MD PhD, Graduate Institute of International and Development Studies, Geneva, Switzerland; École de Santé publique de l'Université de Montréal, Montréal, Canada; and Collège d'Études mondiales, Maison des Sciences de l'Homme, Paris, France

Samuel A Sheku Kargbo MD, MPH, DMed, Ministry of Health and Sanitation, Freetown, Sierra Leone

Daouda Sissoko MD, Institut National de la Sante et de la recherche Médicale, INSERM U1219, Université de Bordeaux, Bordeaux, France.

Iván Darío Vélez MD, MSc, PhD, Programa de Estudio y Control de Enfermedades Tropicales, Antioquias University Medical School, Medellin-Colombia

References

1. World Health Organisation. R&D preparedness for epidemics: A Blueprint for research and development. 2016.
2. World Health Organisation. WHO publishes list of top emerging diseases likely to cause major epidemics [Internet]. 2015. Available from: <http://www.who.int/medicines/ebola-treatment/WHO-list-of-top-emerging-diseases/en/>
3. UNAIDS/WHO. Ethical considerations in biomedical HIV prevention trials [additional guidance point added in 2012] [Internet]. 2012 [cited 2013 Aug 7]. Available from: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2012/jc1399_ethical_considerations_en.pdf
4. UNAIDS/AVAC. Good participatory practice guidelines for biomedical HIV prevention trials 2011 [Internet]. Joint United Nations Programme on HIV/AIDS; 2011 [cited 2013 Aug 7]. Available from: http://www.unaids.org/en/media/unaids/contentassets/documents/unaidspublication/2011/JC1853_GPP_Guidelines_2011_en.pdf
5. UNAIDS. Creating effective partnerships for HIV prevention trials: report of a UNAIDS consultation. 2005.
6. Mills E, Rachlis B, Wu P, Wong E, Wilson K, Singh S. Media reporting of tenofovir trials in Cambodia and Cameroon. *BMC Int Health Hum Rights*. 2005 Aug 24;5:6.
7. Global Campaign for Microbicides. Preventing prevention trial failures: A case study and lessons learned for future trials from the 2004 tenofovir trial in Cambodia. 2009.
8. Global Campaign for Microbicides. Research Rashomon: Lessons from the Cameroon pre-exposure prophylaxis trial site. 2009.
9. Singh JA, Mills EJ. The abandoned trials of pre-exposure prophylaxis for HIV: what went wrong? *PLoS Med*. 2005 Sep;2(9):e234.
10. UNAIDS/AVAC. Good participatory practice guidelines for biomedical HIV prevention trials. 2007.
11. Grant RM, Lama JR, Anderson PL, McMahan V, Liu AY, Vargas L, et al. Preexposure chemoprophylaxis for HIV prevention in men who have sex with men. *N Engl J Med*. 2010 Dec 30;363(27):2587–99.
12. Fuchs JD, Sobieszczyk ME, Hammer SM, Buchbinder SP. Lessons Drawn from Recent HIV Vaccine Efficacy Trials. *J Acquir Immune Defic Syndr* [Internet]. 2010 Dec 15 [cited 2013 Aug 7];55(Suppl 2):S128–31. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC3079543/>
13. Mack N, Kirkendale S, Omullo P, Odhiambo J, Ratlhagana M, Masaki M, et al. Implementing good participatory practice guidelines in the FEM-PrEP preexposure prophylaxis trial for HIV prevention among African women: a focus on local stakeholder involvement. *Open Access J Clin Trials* [Internet]. 2013 Oct [cited 2016 Apr 25];127. Available from: <http://www.dovepress.com/implementing-good-participatory-practice-guidelines-in-the-fem-prep-pr-peer-reviewed-article-OAJCT>

14. Sahay S, Mehendale S. Engaging community to support HIV prevention research. *East J Med EJM*. 2011;16(2):168–77.
15. The Ethics Working Group of the HIV Prevention Trials Network, MacQueen KM, Bhan A, Frohlich J, Holzer J, Sugarman J. Evaluating community engagement in global health research: the need for metrics. *BMC Med Ethics* [Internet]. 2015 Dec [cited 2016 Apr 25];16(1). Available from: <http://www.biomedcentral.com/1472-6939/16/44>
16. Critical Path to TB Drug Regimens. Good participatory practice guidelines for TB drug trials [Internet]. 2012. Available from: <http://cptrinitiative.org/downloads/resources/GPP-TB%20Oct1%202012%20FINAL.pdf>
17. Green LW, Mercer SL. Can public health researchers and agencies reconcile the push from funding bodies and the pull from communities? *Am J Public Health*. 2001 Dec;91(12):1926–9.
18. OECD/DAC. The Paris Declaration on Aid Effectiveness (2005) and the Accra Agenda for Action (2008) [Internet]. Available from: <http://www.oecd.org/dac/effectiveness/34428351.pdf>
19. Cornwall A, Jewkes R. What is participatory research? *Soc Sci Med* 1982. 1995 Dec;41(12):1667–76.
20. Khanlou N, Peter E. Participatory action research: considerations for ethical review. *Soc Sci Med* 1982. 2005 May;60(10):2333–40.
21. Macaulay AC, Commanda LE, Freeman WL, Gibson N, McCabe ML, Robbins CM, et al. Participatory research maximises community and lay involvement. North American Primary Care Research Group. *BMJ*. 1999 Sep 18;319(7212):774–8.
22. Israel BA, Schulz AJ, Parker EA, Becker AB, Community-Campus Partnerships for Health. Community-based participatory research: policy recommendations for promoting a partnership approach in health research. *Educ Health Abingdon Engl*. 2001;14(2):182–97.
23. Macaulay AC, Gibson N, Freeman WL, Commanda LE, McCabe ML, Robbins CM, et al. The community's voice in research. *CMAJ Can Med Assoc J J Assoc Medicale Can*. 2001 Jun 12;164(12):1661–3.
24. Israel BA, Schulz AJ, Parker EA, Becker AB. Review of community-based research: assessing partnership approaches to improve public health. *Annu Rev Public Health*. 1998;19:173–202.
25. Vallely A, Shagi C, Kasindi S, Desmond N, Lees S, Chiduo B, et al. The benefits of participatory methodologies to develop effective community dialogue in the context of a microbicide trial feasibility study in Mwanza, Tanzania. *BMC Public Health* [Internet]. 2007 [cited 2016 Jun 22];7(1):133. Available from: <http://bmcpublihealth.biomedcentral.com/articles/10.1186/1471-2458-7-133>
26. Boga M, Davies A, Kamuya D, Kinyanjui SM, Kivaya E, Kombe F, et al. Strengthening the informed consent process in international health research through community engagement: The KEMRI-Wellcome Trust research programme experience. *PLoS Med* [Internet]. 2011 Sep 13 [cited 2016 May 1];8(9):e1001089. Available from: <http://dx.plos.org/10.1371/journal.pmed.1001089>
27. Vallely A, Lees S, Shagi C, Kasindi S, Soteli S, Kaviti N, et al. How informed is consent in vulnerable populations? Experience using a continuous consent process during the MDP301

- vaginal microbicide trial in Mwanza, Tanzania. *BMC Med Ethics* [Internet]. 2010 [cited 2016 Jun 22];11(1):10. Available from: <http://bmcmethics.biomedcentral.com/articles/10.1186/1472-6939-11-10>
28. World Health Organization. Building resilient health systems in Ebola-affected countries. EXECUTIVE BOARD EB136/INF./5 136th session Provisional agenda item 9.4. 2015.
 29. Thiam S, Delamou A, Camara S, Carter J, Lama EK, Ndiaye B, et al. Challenges in controlling the Ebola outbreak in two prefectures in Guinea: why did communities continue to resist? *Pan Afr Med J*. 2015;22 Suppl 1:22.
 30. Council for International Organizations of Medical Sciences. International Ethical Guidelines for Biomedical Research Involving Human Subjects (draft revision 2016). 2016.
 31. World Health Organization. Ethical Guidance for Managing Epidemic Outbreaks (draft document). 2016.
 32. Gostin LO, Friedman EA, Buse K, Waris A, Mulumba M, Joel M, et al. Towards a framework convention on global health. *Bull World Health Organ*. 2013 Oct 1;91(10):790–3.
 33. Otter JA, Donskey C, Yezli S, Douthwaite S, Goldenberg SD, Weber DJ. Transmission of SARS and MERS coronaviruses and influenza virus in healthcare settings: the possible role of dry surface contamination. *J Hosp Infect* [Internet]. 2016 Mar [cited 2016 Apr 17];92(3):235–50. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0195670115003679>
 34. Wong G, Liu W, Liu Y, Zhou B, Bi Y, Gao GF. MERS, SARS, and Ebola: The role of super-spreaders in infectious disease. *Cell Host Microbe* [Internet]. 2015 Oct [cited 2016 Apr 17];18(4):398–401. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S1931312815003820>
 35. Yen M-Y, Chiu AW-H, Schwartz J, King C-C, Lin YE, Chang S-C, et al. From SARS in 2003 to H1N1 in 2009: lessons learned from Taiwan in preparation for the next pandemic. *J Hosp Infect* [Internet]. 2014 Aug [cited 2016 Apr 17];87(4):185–93. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S019567011400156X>
 36. Porten K, Faensen D, Krause G. SARS outbreak in Germany 2003: workload of local health departments and their compliance in quarantine measures--implications for outbreak modeling and surge capacity? *J Public Health Manag Pract JPHMP*. 2006 Jun;12(3):242–7.
 37. Chan GCT, Koh D. Reviewing lessons learnt of SARS in Singapore during planning for influenza pandemic. *Int Marit Health*. 2006;57(1-4):163–76.
 38. Goldhar J, Adie C, Webb N, Harrison L. The Baycrest SARS experience: the human side. *Aust Health Rev Publ Aust Hosp Assoc*. 2003;26(3):14–8.
 39. Affonso DD, Andrews GJ, Jeffs L. The urban geography of SARS: paradoxes and dilemmas in Toronto's health care. *J Adv Nurs*. 2004 Mar;45(6):568–78.
 40. World Health Organisation. Ethical guidance for managing infectious disease outbreaks (draft). 2016.
 41. Suwantararat N, Apisanthanasarak A. Risks to healthcare workers with emerging diseases: lessons from MERS-CoV, Ebola, SARS, and avian flu. *Curr Opin Infect Dis* [Internet]. 2015 Aug [cited 2016 Apr 17];28(4):349–61. Available from:

- <http://content.wkhealth.com/linkback/openurl?sid=WKPTLP:landingpage&an=00001432-201508000-00011>
42. Ebola haemorrhagic fever in Sudan, 1976. Report of a WHO/International Study Team. *Bull World Health Organ.* 1978;56(2):247–70.
 43. Ebola haemorrhagic fever in Zaire, 1976. *Bull World Health Organ.* 1978;56(2):271–93.
 44. Kennedy SB, Neaton JD, Lane HC, Kieh MW, Massaquoi MB, Touchette NA, et al. Implementation of an Ebola virus disease vaccine clinical trial during the Ebola epidemic in Liberia: Design, procedures, and challenges. *Clin Trials* [Internet]. 2016 Feb 1 [cited 2016 Mar 24];13(1):49–56. Available from: <http://ctj.sagepub.com/cgi/doi/10.1177/1740774515621037>
 45. Gadugah N. Ebola vaccine trial in Ghana will not spread virus-Health Minister. *Ghana\Myjoyonline.com* [Internet]. 2015 Jun 16; Available from: <http://www.myjoyonline.com/news/2015/june-16th/ebola-vaccine-trial-in-ghana-will-not-spread-virus-health-minister.php>
 46. Sissoko D, Laouenan C, Folkesson E, M'Lebing A-B, Beavogui A-H, Baize S, et al. Experimental treatment with Favipiravir for Ebola Virus Disease (the JIKI Trial): A historically controlled, single-arm proof-of-concept trial in Guinea. Lipsitch M, editor. *PLOS Med* [Internet]. 2016 Mar 1 [cited 2016 Mar 24];13(3):e1001967. Available from: <http://dx.plos.org/10.1371/journal.pmed.1001967>
 47. Agnandji ST, Huttner A, Zinser ME, Njuguna P, Dahlke C, Fernandes JF, et al. Phase 1 trials of rVSV Ebola vaccine in Africa and Europe - Preliminary report. *N Engl J Med.* 2015 Apr 1;
 48. The Lancet. An Ebola vaccine: first results and promising opportunities. *The Lancet* [Internet]. 2015 Aug [cited 2016 Mar 28];386(9996):830. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0140673615611771>
 49. Henao-Restrepo AM, Longini IM, Egger M, Dean NE, Edmunds WJ, Camacho A, et al. Efficacy and effectiveness of an rVSV-vectored vaccine expressing Ebola surface glycoprotein: interim results from the Guinea ring vaccination cluster-randomised trial. *The Lancet* [Internet]. 2015 Aug [cited 2016 Mar 27];386(9996):857–66. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0140673615611775>
 50. Ebola ça suffit ring vaccination trial consortium. 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* [Internet]. 2015;351:h3740. Available from: <http://www.ncbi.nlm.nih.gov/pmc/articles/PMC4516343/>
 51. Enria L, Lees S, Smout E, Mooney T, Tengbeh AF, Leigh B, et al. Power, Fairness and Trust: understanding and engaging with vaccine trial participants and communities in the setting up the EBOVAC-Salone vaccine trial in Sierra Leone. submitted;
 52. Folayan MO, Brown B, Haire B, Yakubu A, Peterson K, Tegli J. Stakeholders' engagement with Ebola therapy research in resource limited settings. *BMC Infect Dis* [Internet]. 2015 Dec [cited 2016 Mar 28];15(1). Available from: <http://www.biomedcentral.com/1471-2334/15/242>
 53. Cohen J, Kupferschmidt K. *Infectious Diseases.* Ebola vaccine trials raise ethical issues. *Science.* 2014 Oct 17;346(6207):289–90.

54. Hatfield I, Allison A, Flight L, Julious SA, Dimairo M. Adaptive designs undertaken in clinical research: a review of registered clinical trials. *Trials*. 2016;17(1):150.
55. Folayan M, Brown B, Yakubu A, Peterson K, Haire B. Compassionate use of experimental drugs in the Ebola outbreak. *The Lancet* [Internet]. 2014 Nov [cited 2016 Mar 28];384(9957):1843–4. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0140673614616056>
56. Global health risk framework research and development of medical products: Workshop summary. Natl Academy Pr; 2016.
57. Adebamowo C, Bah-Sow O, Binka F, Bruzzzone R, Caplan A, Delfraissy J-F, et al. Randomised controlled trials for Ebola: practical and ethical issues. *The Lancet* [Internet]. 2014 Oct [cited 2016 Jun 23];384(9952):1423–4. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S0140673614617347>
58. Fitzgerald F, Yeung S, Gibb DM, Baion DE, Pollard A. Ebola vaccination. *The Lancet* [Internet]. 2015 Dec [cited 2016 Mar 28];386(10012):2478. Available from: <http://linkinghub.elsevier.com/retrieve/pii/S014067361501243X>
59. Longini IM, Egger M, Dean NE, Edmunds WJ, Henao-Restrepo AM, study steering group. Ebola vaccination - Authors' reply. *Lancet Lond Engl*. 2015 Dec 19;386(10012):2480.
60. World Health Organization. Developing global norms for sharing data and results during public health emergencies Statement arising from a WHO Consultation held on 1-2 September 2015 [Internet]. 2015 [cited 2016 Mar 28]. Available from: http://www.who.int/medicines/ebola-treatment/blueprint_phe_data-share-results/en/
61. Modjarrad K, Moorthy VS, Millett P, Gsell P-S, Roth C, Kieny M-P. Developing global norms for sharing data and results during public health emergencies. *PLOS Med* [Internet]. 2016 Jan 5 [cited 2016 Mar 28];13(1):e1001935. Available from: <http://dx.plos.org/10.1371/journal.pmed.1001935>
62. Dye C, Bartolomeos K, Moorthy V, Kieny MP. Data sharing in public health emergencies: a call to researchers. *Bull World Health Organ* [Internet]. 2016 Mar 1 [cited 2016 Mar 28];94(3):158–158. Available from: <http://www.who.int/entity/bulletin/volumes/94/3/16-170860.pdf>
63. Clinical Trials Anthropology Platform. Anthropology & Ebola Clinical Research - Working Document. 2014.
64. Rubincam C, Lacombe-Duncan A, Newman PA. Taking culture seriously in biomedical HIV prevention trials: a meta-synthesis of qualitative studies. *Expert Rev Vaccines* [Internet]. 2015 Dec 2 [cited 2016 Mar 24];1–17. Available from: <http://www.tandfonline.com/doi/full/10.1586/14760584.2016.1118349>
65. World Health Organisation. A research and development Blueprint for action to prevent epidemics [Internet]. 2016 [cited 2016 Jun 23]. Available from: http://www.who.int/csr/research-and-development/WHO-R_D-Final10.pdf?ua=1
66. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. The Belmont Report: Ethical principles and guidelines for the protection of human subjects of research. USA Department of Health, Education, and Welfare, Washington, DC; 1979.

67. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use. Guideline for good clinical practice. ICH harmonised tripartite guideline. 2006.
68. World Health Organization. Handbook for Good Clinical Research Practice (GCP): guidance for implementation. 2002.
69. World Health Organization, Special Programme for Research & Training in Tropical Diseases. Good Clinical Laboratory Practice (GCLP). 2009.
70. World Health Organization. Quality assurance of pharmaceuticals: a compendium of guidelines and related materials. Vol. 2, Good manufacturing practices and inspection. 2nd edition. 2007.
71. Community Recommendations Working Group of Community Partners, a global group of community representatives affiliated with the National Institute of Allergy and Infectious Diseases (NIAID) HIV/AIDS clinical trials networks. Recommendation for community involvement in National Institute of Allergy and Infectious Diseases, HIV/AIDS clinical trials research. 2009.
72. Robinson ET, Baron D, Heise LL, Moffett J, Harlan SV. Communications Handbook for Clinical Trials: Strategies, tips, and tools to manage controversy, convey your message, and disseminate results. Microbicides Media Communications Initiative and FHI; 2010.
73. World Medical Association. World Medical Association Declaration of Helsinki: Ethical principles for medical research involving human subjects. Helsinki, World Medical Association General Assembly, 1964; latest amendment at the 59th WMA General Assembly, Seoul. 2008.
74. Council for International Organizations of Medical Sciences. International Ethical Guidelines for Biomedical Research Involving Human Subjects. 2002.
75. Nuremberg Code (1949). Trials of War Criminals before the Nuremberg Military Tribunals under Control Council Law No. 10, Vol. 2, pp. 181–182. US Government Printing Office, Washington, DC.;
76. Nuffield Council on Bioethics. The ethics of healthcare related research in developing countries: a follow-up discussion paper. 2005.
77. Nuffield Council on Bioethics. The ethics of research related to healthcare in developing countries. 2002.
78. United Nations Educational, Scientific, and Cultural Organisation (UNESCO). Universal declaration on bioethics and human rights [Internet]. 2005 [cited 2016 Aug 28]. Available from: <http://unesdoc.unesco.org/images/0014/001461/146180E.pdf>
79. Molyneux CS, Wassenaar DR, Peshu N, Marsh K. 'Even if they ask you to stand by a tree all day, you will have to do it (laughter)...!': Community voices on the notion and practice of informed consent for biomedical research in developing countries. Soc Sci Med [Internet]. 2005 Jul;61(2):443–54. Available from: <http://www.sciencedirect.com/science/article/pii/S0277953604006513>
80. Molyneux C, Peshu N, Marsh K. Understanding of informed consent in a low-income setting: three case studies from the Kenyan Coast. Soc Sci Med. 2004;59:2547–59.

81. Richter LM, Lindegger GC, Abdool Karim Q, Gasa N. Guidelines for the development of culturally sensitive approaches to obtaining informed consent for participation in HIV vaccine-related trials [Internet]. UNAIDS; 1999. Available from: <http://www.saavi.org.za/un aids.pdf>
82. Strauss RP, Sengupta S, Quinn SC, Goepfing J, Spaulding C, Kegeles SM, et al. The role of community advisory boards: involving communities in the informed consent process. *Am J Public Health*. 2001 Dec;91(12):1938–43.
83. Appelbaum PS, Lidz CW, Meisel A. *Informed Consent: Legal Theory and Clinical Practice*. Oxford University Press, New York; 1987.
84. WHO. Infection prevention and control of epidemic-and pandemic prone acute respiratory infections in health care WHO guidelines [Internet]. 2014 [cited 2016 Apr 17]. Available from: http://www.who.int/csr/bioriskreduction/infection_control/publication/en/
85. Philpott S, Heise L, McGrory E, Paxton L, Hankins C, participants in the 2009 GCM/CDC/UNAIDS consultation on standards of prevention in HIV prevention trials. The challenge of defining standards of prevention in HIV prevention trials. *J Med Ethics*. 2011 Apr;37(4):244–8.
86. World Health Organization. Guidance on ethics of tuberculosis prevention, care and control [Internet]. Geneva, Switzerland: World Health Organization; 2010 [cited 2016 Jun 22]. Available from: http://whqlibdoc.who.int/publications/2010/9789241500531_eng.pdf
87. Hayes R, Ayles H, Beyers N, Sabapathy K, Floyd S, Shanaube K, et al. HPTN 071 (PopART): Rationale and design of a cluster-randomised trial of the population impact of an HIV combination prevention intervention including universal testing and treatment – a study protocol for a cluster randomised trial. *Trials* [Internet]. 2014 [cited 2016 Mar 28];15(1):57. Available from: <http://www.trialsjournal.com/content/15/1/57>
88. Hamel MB, Darrow JJ, Sarpatwari A, Avorn J, Kesselheim AS. Practical, legal, and ethical issues in expanded access to investigational drugs. *N Engl J Med* [Internet]. 2015 Jan 15 [cited 2016 Aug 30];372(3):279–86. Available from: <http://www.nejm.org/doi/abs/10.1056/NEJMhle1409465>
89. US National Bioethics Advisory Commission. *Ethical and policy issues in international research: Clinical trials in developing countries. Volume I: Report and recommendations of the National Bioethics Advisory Commission*. 2001.