The Ebola epidemic

Ethics Guidance

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(On behalf of the GHE Unit)
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World Health Organization

Objective

- Overview of the ethical issues identified during the Ebola epidemic and the recommendations provided in response

- Work of WHO in Ethics during Ebola epidemic:

    - Meeting Reports
    - Guidance documents

Background

1. First Meeting of the IHR Emergency Committee: 6-7 August
    - Public Health Emergency of International Concern: **high public health risk posed by the epidemic to all States**
2. On 11 August, WHO convened an Ethics Panel

Ethics Panel - 11 August

Purpose

What are the ethical implications of using unregistered interventions that have not yet been evaluated for safety and efficacy in humans?

Outcome

"In the **exceptional situation of the current Ebola outbreak**, there is an ethical imperative to offer the available unregistered interventions that have shown promising results in the laboratory and in relevant animal models to patients and people at high risk of developing the disease…"

*Moral obligation to collect and share data **rapidly** and **transparently***

*Use of EIs should **not** interfere with containment and supportive care strategies*

Ethics Panel - 11 August

- Departure from the historically evolved system of regulation and governance of therapies and interventions
- Raised further questions/challenges, which requested further guidance

Questions to be answered

1. In **what context** should experimental interventions (EIs) be used?
2. Methodologically, **which type of study designs** could provide interpretable data in situations where placebo controlled trials were either unfeasible or unacceptable to the local population?
3. Should **children and pregnant women** be excluded from these early studies?

Etc. etc.

1. In what context should EIs be used?

- Urgent need to gather sound evidence on safety and efficacy, and limited window of opportunity for research→ **Research setting.**

Research

- **Need to fast track the drug development pathway**
  - Should not equate to cutting corners

WHO Working Group Meetings:11 August; 4-5 Sept 2014; 20-21 Oct 2014
Guidance document: MEURI

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- When outside of research, **avoid term "compassionate use"**
  - Term associated with a presumed benefit
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Compassionate Use?

- Monitored Emergency Use of Unregistered Interventions: **MEURI**

MEURI

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2. Which type of study designs?

- ***All decisions*** *related to use of EI should be aligned with the aim to learn as much as possible, as quickly as possible, without compromising patient care and health worker safety*.

- The use of placebo and randomization may not be feasible or acceptable in the affected countries

- An **adaptive design** may be preferable given that:
  - It has the capacity to yield meaningful and interpretable data **quickly and early in the trial**
  - Study can be **modified** based on early findings
  - Potential to have **high impact on mortality**

WHO Working Group Meetings: 4-5 Sept 2014; 20-21 Oct 2014

3. Inclusion of vulnerable populations?

- May need to reconsider existing guidance on the **exclusion** of:
  - **Children** in trials with potentially effective therapies for Ebola in light of:
    - High risk of mortality from EVD
    - Need to gather data on safety and efficacy in this population
  - **Pregnant women** in trials with potentially effective therapies for Ebola in light of:
    - Same arguments as with children
    - Existing evidence: fetuses and born babies do not survive

Guidance documents: Involvement of Children in Research or MEURI;
Inclusion of pregnant women in clinical research or MEURI

Other issues

- Healthcare workers' obligations
- Data sharing and access; Biobanking
- Developing the notion of MEURI
- Isolation and Quarantine measures
- Priority setting for access to vaccines, treatments and other resources
- Vaccine trials during an epidemic
- Ethics of using Convalescent Whole Blood and plasma

→ **Guidance in progress/to be developed**

Guidance documents: HCW obligations during the Ebola epidemic; MEURI; Vaccine Trials
WHO Working Group Meeting: 4-5 Sept 2014

Use of convalescent whole blood/plasma

- One of the **prioritized** experimental interventions by the Scientific Technical Advisory Committee

- **Specific recommendations** on the use of these interventions:
  - Analysis of ethical issues related to donors, recipients and healthcare workers

- Use of CWB/CP in the field raised **further issues** in relation to ownership and management of the excess of blood/plasma samples

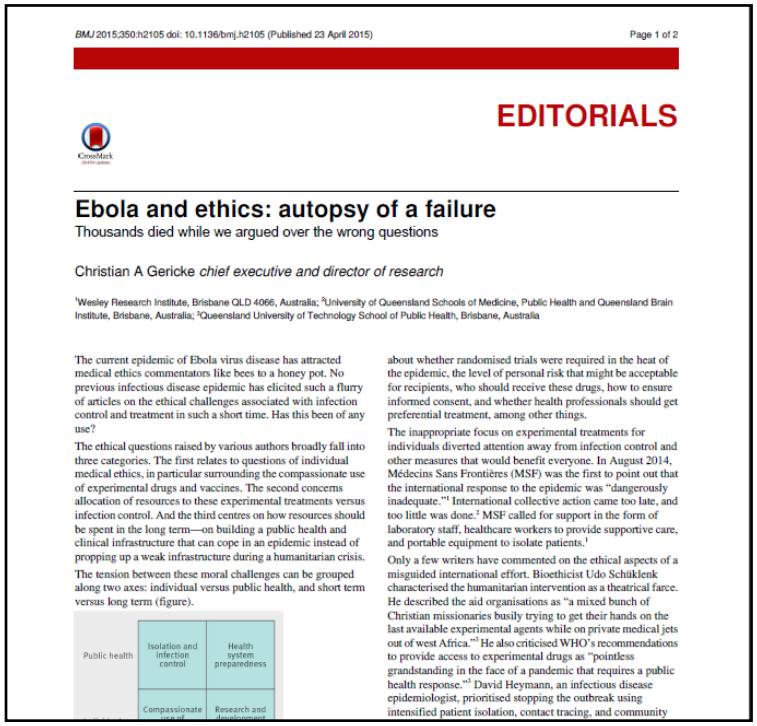
Guidance document: Ethics of using CWB/CP during the Ebola epidemic

Next steps

- Next steps:
  - From Ebola Virus Disease to Epidemics
  - From Research to Public Health Actions

Discussion

- The wrong questions asked?
  - Inappropriate focus on experimental treatments for individuals?
  - New guidance on HCW obligations?



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EDITORIALS

Ebola and ethics: autopsy of a failure

Thousands died while we argued over the wrong questions

Christian A Gericke *chief executive and director of research*

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The current epidemic of Ebola virus disease has attracted medical ethics commentators like bees to a honey pot. No previous infectious disease epidemic has elicited such a flurry of articles on the ethical challenges associated with infection control and treatment in such a short time. Has this been of any use?

The ethical questions raised by various authors broadly fall into three categories. The first relates to questions of individual medical ethics, in particular surrounding the compassionate use of experimental drugs and vaccines. The second concerns allocation of resources to these experimental treatments versus infection control. And the third centres on how resources should be spent in the long term—on building a public health and clinical infrastructure that can cope in an epidemic instead of propping up a weak infrastructure during a humanitarian crisis.

The tension between these moral challenges can be grouped along two axes: individual versus public health, and short term versus long term (figure).

about whether randomised trials were required in the heat of the epidemic, the level of personal risk that might be acceptable for recipients, who should receive these drugs, how to ensure informed consent, and whether health professionals should get preferential treatment, among other things.

The inappropriate focus on experimental treatments for individuals diverted attention away from infection control and other measures that would benefit everyone. In August 2014, Médecins Sans Frontières (MSF) was the first to point out that the international response to the epidemic was "dangerously inadequate."[1] International collective action came too late, and too little was done.[2] MSF called for support in the form of laboratory staff, healthcare workers to provide supportive care, and portable equipment to isolate patients.[1]

Only a few writers have commented on the ethical aspects of a misguided international effort. Bioethicist Udo Schüklenk characterised the humanitarian intervention as a theatrical farce. He described the aid organisations as "a mixed bunch of Christian missionaries busily trying to get their hands on the last available experimental agents while on private medical jets out of west Africa."[3] He also criticised WHO's recommendations to provide access to experimental drugs as "pointless grandstanding in the face of a pandemic that requires a public health response."[3] David Heymann, an infectious disease epidemiologist, prioritised stopping the outbreak using intensified patient isolation, contact tracing, and community

Thank you!

Acknowledgements:

Abha Saxena, Andreas Reis, Marisol Guraiib

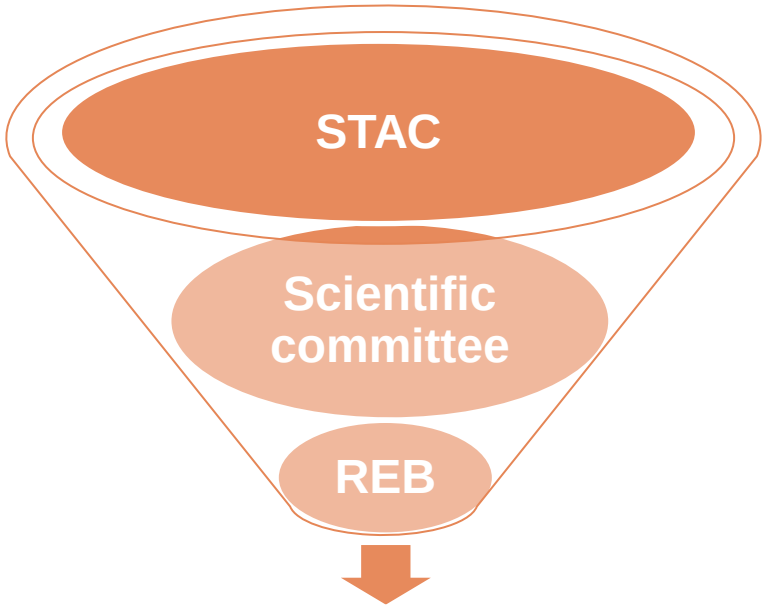
Global Health Ethics, WHO-HQ

Contact: delafuentenunezv@who.int

The resulting actions from August 11th

Research Protocols

In less than 5 months, 47 **registered trials** in ICTRP, of which 17 are on treatment, 28 on prevention and 2 on diagnostics.



Drugs and Vaccines in approved trials

Compassionate Use?

Some interventions that were **not** approved, either scientifically or ethically, were given to patients on the basis of compassionate use.

X

Discussion on Study Designs

Study design	Advantages	Disadvantages
RCT "The Gold Standard"	• Achieve answer quickly with relatively small sample size • Remove selection bias and control for variation	• Unethical? Unfeasible? Unsafe? • No consensus on comparator • Risk of poor compliance
Stepped Wedge Design	• Randomization by cluster may be more acceptable • Potential higher compliance • Staggering may make it easier to implement • Realistic mirror of availability of drugs	• Logistical difficulties • Complex statistical analysis • Need to control for temporal trends to mitigate bias • Risk of "gravitation"
RCT with stepped roll-out	• Can be rolled out more rapidly than RCT • Adaptability • Randomization • Maximum follow-up time	• Requires a control group • Logistical challenges • Complex randomization process
Cluster Randomized Trial	• Greater acceptability? • Less complex • Includes control group	• Larger sample sizes? • Complex statistical analysis • Risk of "gravitation"
Single Arm non-comparative study	• Early availability of control data • Relatively small sample size • More acceptable? • Easier implementation	• Higher potential risk for bias • Lack of consent from historical control group

ii. Research with EIs and Study Design

- **Ethical considerations** in selecting a particular design and a particular intervention:

Drug	Design	Site	Participant	Institutional
• Prior knowledge • Number of doses available now/future • Ease of admin and monitoring • Risk to healthcare workers • Additional support?	• Number of participants required • Time required • Bias (internal consistency) • Complexity	• Human resources • Infrastructure	• Equity • Access • Distribution of benefits and risks • Acceptability • Complexity of community engagement	• Capacity for ethics review

iv. EIs and vaccine trials

- Different ethical considerations between prophylaxis and therapeutics :
  - Healthy, uninfected individuals vs. Infected Individuals
  - Low vs. High risks to healthcare workers

- Different ethical considerations between pre-exposure prophylaxis and post-exposure prophylaxis
  - Presumably uninfected individuals vs. infected individuals
  - Low vs. High risks to healthcare workers

- Reconsideration of study designs

Guidance document: Ethics of Vaccine Trials and different study designs

Ethics Consultation: Advisors

Name	Affiliation	Country
Prof M. Selgelid	Director Centre for Human Bioethics, Monash University	Australia
Dr. P. Calain (Chair)	Unité de Recherche, MSF	Switzerland
Prof. A. Toure	Head of Immunology Department, Pasteur Institute	Senegal
Prof. R. Upshur	Canada Research Chair in Primary Care Research; Professor, University of Toronto	Canada
Prof. P. Smith	Professor of Tropical Epidemiology, LSHTM	UK
Dr. H.B. Ndagije	Head of the Drug Information Department in the Ugandan National Drug Authority	Uganda
Prof J. Farrar	Director, Wellcome Trust	UK
Prof R. Ida	Member of the Expert Panel on Bioethics	Japan
Ms. J.Thomas	Patient Safety Champion	USA
Dr. J.P. Beca	Professor, Bioethics Center at Universidad del Desarrollo	Chile
Prof. T. Madani	Professor of internal medicine and infectious diseases	Saudi Arabia
Dr. M. Danis	Head, Sect. on Ethics & Health Policy (NIH)	USA

Ethics Consultation: Resource Persons

Name	Affiliation	Country
Dr. S. Monroe	CDC, US-FDA	USA
Prof. L.Borio	US-FDA	USA
Dr. F.Hayden	U Virginia	USA
Dr. D. Baush	U.S. Naval Medical Research Unit No.6 Lima	Peru

Questions to be answered

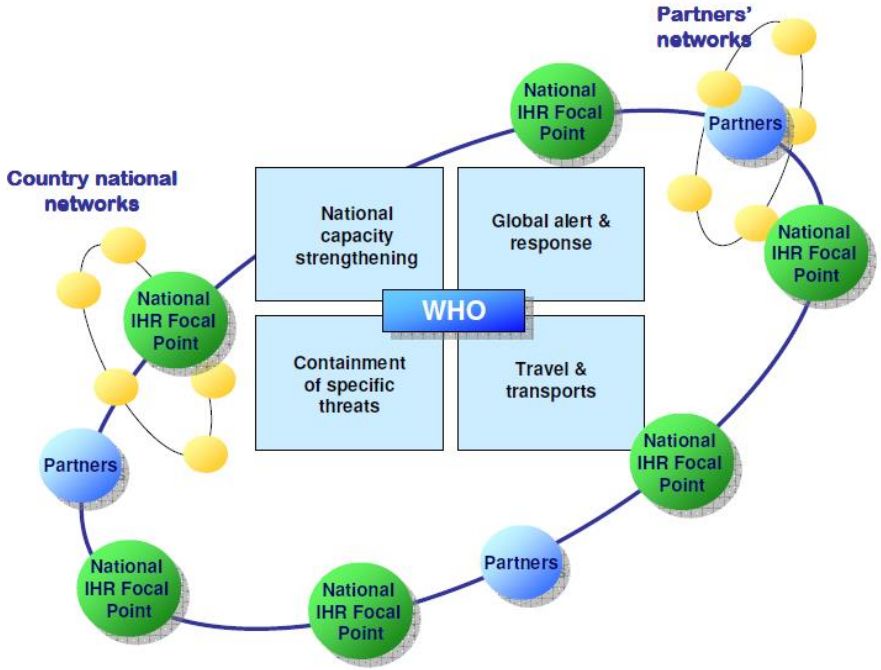
1. Under what conditions could potential therapeutic agents be given outside of a research context?
2. How could the drug development pathways be ethically fast-tracked?
3. Would placebo-controlled trials be acceptable under the prevailing circumstances?
4. Given the scarce data on efficacy and safety of the proposed interventions, and the moral duty to protect vulnerable populations from harm and exploitation, should children and pregnant women be excluded from these early studies?
5. Would the same ethical considerations apply to potential therapeutics and vaccines?

Questions to be answered

- Most of the questions can be broadly grouped under **Research Ethics**
    1. Trial design
    2. Inclusion of vulnerable populations in research
    3. Prioritization of research

- The discussion is compounded by at least two factors:
    -Early stage experimental interventions
    -Outbreak context

Figure 3.1
International public health security: a global network of national health systems and technical partners, focused on four major areas of work, coordinated by WHO

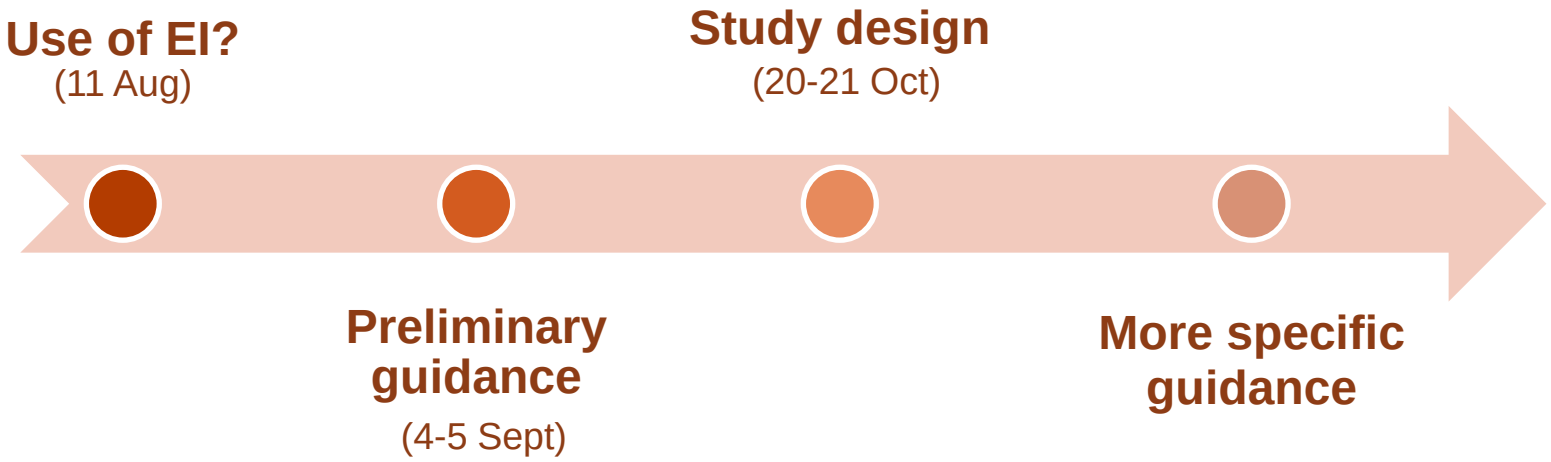


Core functions of the IHR

The IHR help countries to prevent, detect, inform about and respond to public health events in a facilitated manner.

Conclusion

- Next steps:
  - From Research to Public Health Action
  - From EVD to Epidemics
- Guidance development chronology:



Next steps

- From EVD to Epidemics
- From Research to Public Health Actions

i. In what context should EIs be used?

- Urgent need to gather sound evidence on efficacy and safety, and limited window of opportunity for research→ **Research setting.**

Research

- **Need to fast track the drug development pathway**
  - Should not equate to cutting corners
  - Guidance needed for fast-tracking ethics review

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Guidance document: MEURI

i. In what context should EIs be used?

- When outside of research, **avoid term "compassionate use"**

  - Term associated with a presumed benefit and a concurrent clinical trial
  - Does not reflect the urgent need to collect data

Compassionate Use?

- Monitored Emergency Use of Unregistered Interventions: **MEURI**

  - Denotes emergency
  - Reflects urgent need to gather data
  - No presumed benefit associated with the term

MEURI

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