Emergency use of Unproven Interventions

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Origins and Purpose of the Guidance

- Impetus: discussions at WHO about ethical issues raised by the Ebola outbreak in West Africa
- Similar discussions took place in other global infectious disease outbreaks (e.g., SARS, pandemic influenza, and MDR-TB)
- Each time, the focus has been on specific issues raised by the particular outbreak, without considering how the issues might have changed if the epidemiological circumstances had been different
- Goals of this guidance:
  - Focus on the cross-cutting ethical issues that apply to outbreaks generally
  - Examine how these principles can be adapted to different epidemiological and social circumstances

Methodology

Review and synthesis of existing documents

—All WHO ethics guidance related to epidemics
—Selected English-language guidance from official governmental bodies, preferably at national level
—Selected guidance/position papers from professional associations, advisory commissions, academics

Deliberations by expert working group (Dublin, May 2015)

Draft of guidelines produced and circulated to expert working group for comments

Deliberations by broader group of experts and stakeholders (Prato, November 2015)

New draft produced and circulated for broad peer review

Documents Reviewed

General

World Health Organization, Research Ethics in International Epidemic Response (2009)
Institute of Medicine, Guidance for Establishing Crisis Standards of Care for Use in Disaster Situations: A Letter Report (2009)
Ethics Subcommittee of the Advisory Committee to the Director, U.S. Centers for Disease Control and Prevention, Ethical Guidance for Public Health Emergency Preparedness and Response: Highlighting Ethics and Values in a Vital Public Health Service (2008)

Ebola

World Health Organization, Ethics of Vaccine Trials and the Different Strategies under Consideration (Ring Vaccination, Health Workers etc.) as These Trials Get Underway (2015)
World Health Organization, Involvement of Children as Research or MEURI Participants during the Ebola Epidemic (2015)
World Health Organization, Ethics of Using Convalescent Whole Blood and Convalescent Plasma during the Ebola Epidemic (2015)
Presidential Commission for the Study of Bioethical Issues, Ethics and Ebola: Public Health Planning and Response (2015)
American College of Emergency Physicians, the Emergency Nurses Association, and the Society for Academic Emergency Medicine, Ethical Issues in the Response to Ebola Virus Disease in United States Emergency Departments (2015)
World Health Organization, Ethical Considerations for Use of Unregistered Interventions for Ebola Virus Disease (2014)
World Health Organization, Ethical Issues Related to Study Design for Trials on Therapeutics for Ebola Virus Disease (2014)
U.S. Centers for Disease Control and Prevention, Interim U.S. Guidance for Monitoring and Movement of Persons with Potential Ebola Virus Exposure (2014)

Pandemic Influenza

Ethics Subcommittee of the Advisory Committee to the Director, U.S. Centers for Disease Control and Prevention, Ethical Considerations for Decision Making Regarding Allocation of Mechanical Ventilators during a Severe Influenza Pandemic or Other Public Health Emergency (2011)
U.S. Veterans Health Administration, Meeting the Challenge of Pandemic Influenza: Ethical Guidance for Leaders and Health Care Professionals in the Veterans Health Administration (2010)
French National Consultative Ethics Committee for Health and Life Sciences, Ethical Issues Raised by a Possible Influenza Pandemic (2009)
World Health Organization, Ethical Considerations in Developing a Public Health Response to Pandemic Influenza (2007)
Ethics Subcommittee of the Advisory Committee to the Director, U.S. Centers for Disease Control and Prevention, Ethical Guidelines in Pandemic Influenza (2007)
Nigerian Integrated National Avian and Pandemic Influenza Response Plan (2007-2009)
New York State Task Force on Life and the Law, Allocation of Ventilators in an Influenza Pandemic: Planning Document (2007)
UK Department of Health, Responding to Pandemic Influenza: The Ethical Framework for Policy and Planning (2007)
New Zealand National Ethics Advisory Committee, Getting Through Together: Ethical Values for a Pandemic (2007)
Swiss Influenza Pandemic Preparedness Plan (2006)
Finish National Advisory Board on Health Care Ethics, Ethical Considerations Related to Preparedness for a Pandemic (2005
University of Toronto Joint Centre for Bioethics, Stand on Guard for Thee: Ethical Considerations in Preparedness Planning for Pandemic Influenza (2005)

Endemic Infectious Diseases

World Health Organization, Guidance on Ethics of Tuberculosis Prevention, Care, and Control (2010)

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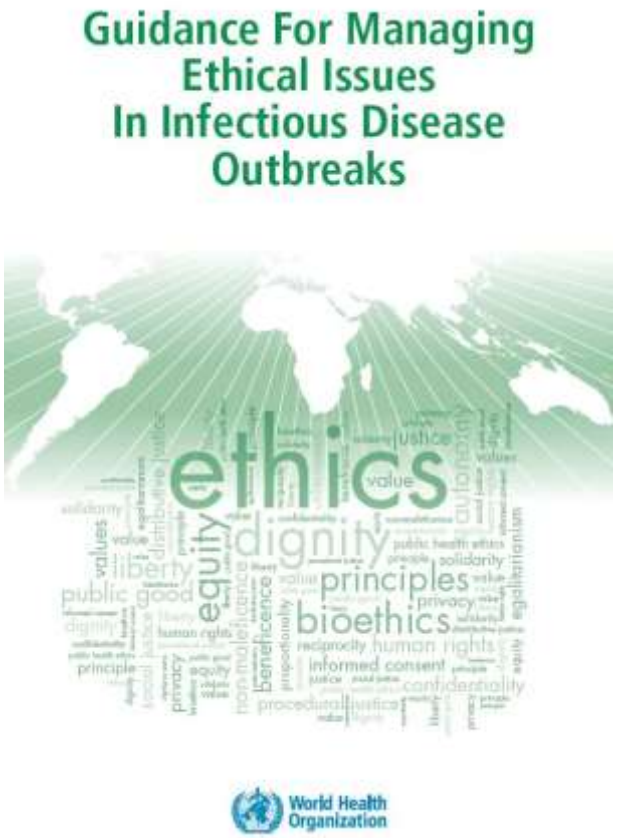

Who is this guidance for?

- Policy makers
- First responders
- Researchers/IRBs
- Public health officials
- Data collectors
- Civil Society…….
- Ministries of health
- Ministries of Agriculture
- Highly developed countries, middle income countries and low income countries
- Surveillance and Public health officials
- Institutions responsible for setting up rapid response teams
- National response teams
- GOARN/GOARN partners

MEURI

Monitored Emergency Use of Unregistered and Experimental Interventions

The Ethics Panel of August 2014

- On 11 August 2014, in the context of the ongoing Ebola outbreak, WHO organized a consultation to consider and assess the ethical implications for clinical decision-making of the use of unregistered interventions that have shown promising results in the laboratory and in animal models but have not yet been evaluated for safety and efficacy in humans.
- A panel of 12 members was invited to advise the WHO Director-General during a 3-h panel discussion, held by teleconferencing.
- Varied background, expertise and geographical representation.
- The expertise of the panelists included: bioethics, scientific research methods, Ebola research, experience in Ebola management, experience in humanitarian crises, patient safety advocacy and regulation of therapeutics.

The starting point

- 1. Is it ethical to use unregistered interventions that have shown promising results in the laboratory and in animal models but have unknown adverse effects in humans
  - for *possible treatment* of people who are infected? If yes, what criteria and conditions must be satisfied before they can be used?
  - for prophylaxis in people who are exposed but who show no signs of disease (i.e. *post-exposure prophylaxis*)? If yes, what criteria and conditions must be satisfied before they can be used?
  - for prophylaxis in people who may be exposed (i.e. *pre-exposure prophylaxis*)? If yes, what criteria and conditions must be satisfied before they can be used?

- 4. If it is ethical to use unregistered interventions that have shown promising results in the laboratory and in animal models under the circumstances described above, what criteria should guide the choice of intervention? And who should receive priority for treatment or prevention?

In the particular context of the current Ebola outbreak in West Africa….

- It is ethically acceptable to offer unproven interventions that have shown promising results in the laboratory and in animal models but have not yet been evaluated for safety and efficacy in humans as potential treatment or prevention.
- Ethical, scientific and pragmatic criteria must guide the provision of such interventions. **The ethical criteria** include transparency …., fairness, promotion of cosmopolitan solidarity, informed consent, freedom of choice, confidentiality, respect for the person, preservation of dignity, involvement of the community and risk–benefit assessment.
- ……..those involved have a **moral obligation to collect and share all the scientifically relevant data generated.**
- Researchers have a **moral duty to evaluate these interventions (for treatment or prevention) in clinical trials** that are of the best possible design in the current exceptional circumstances of the West African Ebola outbreak, in order to establish the safety and efficacy of the interventions or to provide evidence to stop their use. Continuous evaluation should guide future interventions.

Ethics Working Group

- Ethical duty to conduct research

……primarily with the goal of learning as much as we can and as fast as we can.

- Ethical duty to avoid therapeutic misconception
- Ethical duty to respond promptly to research results

Ethics Working Group - Research

- Research during an epidemic is an ethical imperative
- Clinical equipoise is a moving target
- Risk of therapeutic misconception is very high
- **Compassionate use is a misnomer - MEURI**
- Informed consent remains the cornerstone of research
- Equitable distribution of scarce experimental treatments is challenging
- There is an ethical imperative for data collection and sharing in real time

MEURI (…..Is not Research)

- Outbreak characterised by a high mortality
- No proven effective treatment exists
- It is not possible to initiate clinical studies immediately
- Preliminary data to support efficacy and safety – scientific advisory body (Positive risk benefit ratio)
- Regulatory/National approval and ethics approval
- Risks are minimised
- Informed consent
- Use is monitored, and results are shared in a timely manner

Ethical justification for MEURI

- MEURI is justified by the ethical principle of respect for patient autonomy — i.e. the right of individuals to make their own risk–benefit assessments in light of their personal values, goals and health conditions.

- It is also supported by the principle of beneficence — providing patients with available and reasonable opportunities to improve their condition, including measures that can plausibly mitigate extreme suffering and enhance survival.

Scientific basis for MEURI

Countries should not authorize MEURI unless it has first been recommended by an appropriately qualified scientific advisory committee especially established for this purpose.

This committee should base its recommendations on a rigorous review of all data available from laboratory, animal and human studies of the intervention to assess the risk–benefit of MEURI in the context of the risks for patients who do not receive MEURI.

Guiding ethical principles for MEURI

- Same as for drug development clinical trials
- Ethical oversight – even if it is not considered research
- Effective resource allocation
- Minimizing risks
- Collection and sharing of meaningful data
- Informed Consent
- Community Engagement
- Fair distribution in the face of scarcity

Two examples of MEURI

- Safety Monitoring for Emergency Use of Favipiravir in Pregnant Women With Ebola Virus Disease
- MIL77 in Monitored Emergency Use of Unregistered Intervention (MEURI) for Patients with Ebola Virus Disease

Thank You