Ethics Perspective on Proposed Emergency Use of Vaccine in Affected Countries in Parallel with Phase 2 Clinical Trials

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Background

- Panel on Ethical Considerations for Use of Unregistered Interventions for Ebola Viral Disease (11 August 2014)
- Consultation on Potential Ebola Therapies and Vaccines (4-5 August 2014)
  - Ethics Working Group, Pre-Meeting (3 August 2014)
Panel on Ethical Considerations for Use of Unregistered Interventions for Ebola Viral Disease (11 August 2014):

- ethically acceptable to use promising unregistered interventions in exceptional circumstances of current Ebola emergency so long as certain conditions are met:
  - Transparency, fair distribution, informed consent and freedom of choice, confidentiality, involvement of the community, etc.
  - Use should be based on best possible risk/benefit assessment

- There “is moral obligation to collect and share all scientifically relevant data generated, including from treatment provided for “compassionate use” (access to an unapproved drug outside a clinical trial), in order to establish the safety and efficacy of the interventions.”
  - Highlighted need for further consideration of study design

See:  http://apps.who.int/iris/bitstream/10665/130997/1/WHO_HIS_KER_GHE_14.1_eng.pdf?ua=1
Consultation on Potential Ebola Therapies and Vaccines (4-5 August 2014)

“The recipients of experimental interventions, locations of studies, and study design should be based on the aim to learn as much as we can as fast as we can without compromising patient care or health worker safety, with active participation of local scientists, and proper consultation with communities.”

(See “Statement on the WHO Consultation on Potential Ebola Therapies and Vaccines”:
Ethical considerations

Resolution of key ethical issues (e.g., allocation of scarce resources) partly depends on state of knowledge regarding intervention(s) in question:

– Is there true equipoise or reason to believe/have confidence that the intervention in question is beneficial?

Note:

- Difficulty translating from animal studies
- Whether or not at equipoise is a scientific (rather than ethical) question
  – But perhaps such questions are themselves scientifically contentious
Language/communication

- “Compassionate” versus “emergency” use

  - “Compassionate use” often (partly) defined as use where trial participation is impossible. (This precludes key question: Should use of unregistered med be compassionate use or part of a study?)
  - “Compassionate use” seems to imply benefit or presumption thereof (which is inappropriate if situation involves true equipoise).
    - “Compassionate use” sounds like something it would be unfortunate to miss out on.

My preference:
“Monitored Emergency Use of Unregistered Intervention”
Allocation of limited resources

- Standard considerations in pandemic plans and ethical analysis thereof:
  - Potentially competing aims:
    - Utility (avert most DALYs or save most lives)
    - Equality/fairness
Allocation of limited resources

- Standard considerations in pandemic plans and ethical analysis thereof:
  - Commonly prioritized groups:
    - Healthcare workers/emergency personnel
      - Reciprocity
      - Utility
    - Children
      - “Fair innings” argument
      - Utility (more DALYs averted)
Allocation of limited resources

- Standard considerations in pandemic plans and ethical analysis thereof:

  → Assumes intervention in question is beneficial. Does not apply to situation of pure equipoise. (Things change once we move from equipoise to confidence in safety/efficacy.)
Allocation of limited resources

In situation of pure equipoise (and thus no assumption of benefit of intervention in question), there are other reasons to prioritise health workers in particular:

1. Aim to learn as much as we can as fast as we can about efficacy of vaccine—high risk of exposure in this group (like challenge study)

2. Health workers best able to give informed consent (given highest rates of literacy in affected countries and special knowledge r/e medicine in particular)
Allocation within/between countries?

In situation of pure equipoise: again aim should be to learn as much as we can as fast as we can without compromising patient care or health worker safety.

→ Where best able to collect data and/or monitor use via proper scientific study that will shed light on safety/efficacy (without compromising patient care via diversion of resources): countries w/ high burden; countries w/ adequate infrastructure, etc.

Is this fair, r/e those left out? In situation of pure equipoise, we should not assume anyone is being deprived of something that should be considered beneficial. (Things change once we move from equipoise to confidence in safety/efficacy.)
Emergency Use in Controlled Study?

- Placebo
  - Ethically problematic?
    - For study of experimental treatments of patients
    - For study of vaccine (pre-exposure)
      - Less, but perhaps still, problematic (especially in case of health workers who are less likely to assume intervention is protective)

But:

- PRCTs more resource intensive (and thus more likely to compromise care)?
- Cultural perceptions will be hard to manage (even in case of vaccine)?
- Placebo may be unnecessary given other kinds of (controlled) studies that will provide “interpretable data”? 
Ethics and Regulation

Regulators should not require unethical studies as a condition of registration/licensing. Aim to accommodate regulators should not be basis for conducting studies that are more-rigorous-than-necessary (for scientific confidence) or more-rigorous-than-ethically-acceptable. Like ethics, regulation should be flexible r/e exceptional/emergency circumstances.

Regulators require “interpretable data”. As interpretability comes in degrees, regulators must be consulted during study design.
Emergency Use in Controlled Study?

- Whether or not placebo controlled, emergency use in some kind of controlled/interpretable study is ethically imperative if possible (without compromising care and/or health worker safety):
  - Only way to gain efficacy data (which does not seem to be part of current plan)

→ It would be a shame to fail to gain such information during outbreak/epidemic (which is only time such knowledge can be gained).

→ Note this also raises questions about why phase 2/3 “trials” are planned in unaffected states—i.e., we then learn less about key feature of vaccines (rather than learning as much as we can as fast as we can).
Key points and concluding remarks

- Ethical issues (e.g., allocation) depends on state of knowledge re intervention in question.
- During equipoise should not assume intervention is beneficial—aim should be to learn as much as we can about safety/efficacy as fast as we can without compromising patient care or health worker safety.
- Importance of community engagement and transparency re:
  - Who is making decisions
  - Rationale behind decisions

→ Special bodies/commissions should be established within countries.