Responsiveness Requirement Defended

Some critical objections and replies

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What is it?

• What is the “responsiveness requirement”
  • Recognition that “Safari” or “parachute” research is unethical
    • Arrive for safari, pack up tents and leave nothing behind
      • Except for refuse and trash
I am going to succeed
sex can wait

ngoba...likusasa ngelami

AIDS can kill you and your dreams.

NERCHA
Where did it originate?

• First known appearance
  • CIOMS 1993 *International Ethical Guidelines for Biomedical Research Involving Human Subjects*
    • Stated in Guideline 8, *Research involving subjects in underdeveloped communities*

• Before undertaking research involving subjects in underdeveloped communities,...the investigator must ensure that
  • Persons in underdeveloped communities will not ordinarily be involved in research that could be carried out reasonably well in developed communities;
CIOMS 1993 Guideline 8

- Continued
  - The research is responsive to the health needs and the priorities of the community in which it is to be carried out
  - ...consent of the individual subjects
  - ...an ethical review committee that has among its members or consultants persons who are thoroughly familiar with the customs and traditions of the community
  - The statement of Guideline 8 itself makes no mention of making products “reasonably available”
How to interpret ‘responsiveness’?

- A former colonial power conducted research on malaria in one of its tropical colonies
  - Malaria was (and still is) a major public health problem in the country
    - However, the sponsoring government never intended to make a successful prevention or treatment available to the population
    - Their objective was to find a product that could be used by the army and civilians stationed in the country
Commentary under Guideline 8

• ....The research conducted in underdeveloped communities should be responsive to the health needs and priorities of those communities....If any product is to be developed, such as a new therapeutic agent, clear understanding should be reached among investigators, sponsors, representatives of the collaborating countries, and community leaders about what the community is to expect and what can or cannot be provided during and at the close of the research. Such understanding must be reached before the research is begun, to ensure that the research is truly responsive to the priorities of the community.
CIOMS 2002 revision: Guideline 10

- Before undertaking research in a population or community with limited resources, the sponsor and the investigator must make every effort to ensure that:
  - the research is responsive to the health needs and the priorities of the population or community in which it is to be carried out; and
  - any intervention or product developed, or knowledge generated, will be made reasonably available for the benefit of that population or community.

[Also in CIOMS 2009 Guidelines for Epidemiological Studies]
Two inseparable points

- “Responsiveness” requirement goes hand-in-hand with “reasonable availability” requirement
  - Responsiveness is easier to unpack than reasonable availability
    - Some have argued that “reasonable availability” is too strong a requirement
      - It would drive away sponsors
    - Others have contended that it is too weak
      - Developing countries may never otherwise benefit

- Authors of the Fair Benefits” framework attack “reasonable availability” with a series of specious arguments
Fair Benefits Critique

- In cases in which the risks to subjects are minimal and the benefits to sponsors are also minimal, it could be unjust to require the sponsors to make a successful product available to the population
Reply to this criticism

- This mistakes the purpose of the ethical requirement
  - The amount of benefit that a sponsor receives is not relevant to the requirement that the community should receive fair benefits
  - Moreover, the level of risks that the subjects undergo is not relevant to the requirement that the community should receive fair benefits
An example

- The majority of vaccine trials pose low risks to subjects, especially in phase III
- These vaccine trials normally do not provide great profits to the sponsors
- However, there is wide agreement that vaccines are an example of the type of product that ought to be available to the community or the country following a successful trial
Fair Benefits Critique

- A prior agreement to provide a specific product can constrain the population instead of benefiting it
  - The population would have to use this specific product even though a better product may come along later
  - Therefore, it is not just to require people to use a product that may be inferior to another product that becomes available later
Reply to this criticism

• The solution to this problem is to establish appropriate conditions beforehand
  • The several parties can negotiate an agreement or contract that says what ought to happen in such cases
• In addition, a similar agreement should be made in research that will be carried out later
  • The population can then receive the product that is demonstrated to be superior
Responsiveness

- CIOMS Commentary on Guideline 10
  - It is not sufficient simply to determine that a disease is prevalent in the population and that new or further research is needed: the ethical requirement of “responsiveness” can be fulfilled only if successful interventions or other kinds of health benefit are made available to the population
  - Responsiveness is thus tied to “reasonable availability” of products developed or knowledge generated
Declaration of Helsinki 2008

• Paragraph 17
  • Medical research involving a disadvantaged or vulnerable population or community is only justified if the research is responsive to the health needs and priorities of this population or community and if there is a reasonable likelihood that this population or community stands to benefit from the results of the research
  • Implication is that responsiveness requirement does not hold for research in which the population or community is not vulnerable or disadvantaged
Criticisms

- Numerous criticisms in the bioethics literature of the “responsiveness” requirement
- Critiques range over views that the requirement is
  - Unnecessary
  - Too burdensome
  - Impossible to fulfill
  - It has some merit but is too vague to understand how to implement it
Requirement Unnecessary

• Objection
  • As long as an investigation is carried out in compliance with the basic rules requiring a favorable benefit-risk ratio, properly obtained informed consent, and other protections of the rights and welfare of human subjects, there is no further need to ensure responsiveness to the health needs in the place where the research is being conducted.

• Reply
  • This is a minimalist view of ethics. “What was good enough in the past is good enough in the present and future.”
Too burdensome
Too burdensome

- Objection
  - If “responsiveness” requires sponsors of research to provide or pay for success products of research in developing countries
    - It is unrealistic to impose this financial burden
  - If “responsiveness” requires host country governments to provide successful products after a trial is completed
    - They will be unable to afford it
- Reply
  - No single institution, organization, or government should be responsible for making products “reasonably available.” An arrangement for shared responsibility should be negotiated
Precludes rare disease research

- Objection
  - Responsiveness requirement refers to “health needs and priorities” of developing countries. But a country may have a small number of people suffering from a rare disease, which would then not be a “health priority” because of its rarity.

- Reply
  - The number of people suffering from a disease is only one way of determining health priorities. A health priority may also stem from the severity of a disease, its disabling or stigmatizing features. These may be other reasons a country may invoke to determine priority.
    - Examples: lymphatic filariasis, guinea worm disease
Guinea worm disease
Lymphatic filariasis
“Free rider” problem

• Objection
  • The responsiveness requirement does not have legal enforceability.
    • Therefore, the requirement could privilege those communities who choose not to abide by it and penalize those who hold fast by refusing to host unresponsive research.

• Reply
  • Most international ethical guidance lacks legal enforceability. The requirement imposes a *moral* obligation on sponsors regarding what research to conduct and where to conduct it.
Free riders
Requirement insufficient

• Objection
  • Responsiveness alone cannot systematically prevent exploitation of developing countries, promote their interests and preferences, and meet their most pressing and unmet health needs.

• Reply
  • This is obviously true. It shows only that the responsiveness requirement is not an ethically sufficient condition for multinational research. It does not show that the requirement is not ethically necessary.
All-or-nothing game

• Objection
  • Requirement assumes that countries are choosing between a responsive study and an unresponsive study. But if the choice is between hosting unresponsive research or no research at all, the responsiveness requirement might force developing countries to forgo all research and any accompanying benefits.

• Reply
  • Countries are not given a menu of options. The requirement imposes a moral obligation on sponsors regarding what research to conduct and where to conduct it.
Reductio ad absurdum

• Objection
  • If it is obligatory for investigators to conduct their research in developing countries with great health needs, then it is counterproductive for researchers to do any research whatsoever in developed communities. In that case, it is surely better for researchers to conduct “unresponsive” research in developing countries than to forgo that research entirely.

• Reply
  • Ridiculous objection. Same as previous reply. The requirement imposes a moral obligation on sponsors regarding what research to conduct and where to conduct it.
Early phases of research

• Objection
  • The early phases of research do not yield a product. Therefore, the “reasonable availability” requirement is inapplicable.

• Reply
  • This simply underscores the importance of the “responsiveness” requirement. When early phases of research are conducted in developing countries, they must be responsive to the health needs of the population as a precursor to later research that may yield successful products.
Health needs and priorities

- Must ‘responsiveness’ address health needs that are also health priorities of the host community?
  - Priorities are harder to determine than needs
  - Disagreement may exist regarding which priorities are highest
  - No clear methodology for determining priorities
  - Problem of “who decides”?  
    - Ministry of health in developing country
    - Community where research is to be carried out
    - Researchers or sponsors
Health needs

- Developing countries have numerous health needs
  - Research alone is insufficient to meet those needs
- What criteria should be used for determining which needs are most important
  - Urgency of meeting needs?
  - Numbers of people in population who have the need?
  - Likelihood of implementing successful results of research in the community or country?
  - Some combination of the above
A distinction [HPTN Guidance]

- If a course of action is described as an *ethical obligation* (expressed in terms such as 'should', 'must' or 'will'), then normally the action should be done, and while exceptions to that course of action are permissible, these exceptions require a strong ethical justification.

- A course of action described as an *ethical aspiration* (expressed in terms such as 'making good faith efforts') implies that following the course of action is admirable or commendable – a matter of pursuing important ethical ideals – but is not required.
HPTN Guidance Point 15
Provision of successful research interventions

- HPTN research seeking to establish the efficacy of an intervention must have a preliminary plan regarding the provision of successful interventions to research participants and communities.
  - Status: *Ethical obligation* (plans regarding the provision of successful interventions to participants) and *ethical aspiration* (provision of successful interventions to participants, communities and at-risk populations)
  - Responsible and accountable: Sponsor, site Principal Investigator, local partners, protocol team
South African MRC Guidelines

11.4.1 Commencement of research
- No research shall be undertaken until Research Ethics Committees of all collaborating institutions have given ethics approval to the research.
  - Before granting ethics approval, such a Research Ethics Committee shall consider whether the study findings can, and will, be incorporated into the local healthcare system.

11.4.3 Justification
- There must be clear potential benefit to the community being researched.

11.4.4 Benefit to host country
- There should be benefit - other than pure financial gain - to a host country community in which research is undertaken, such as access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study.
Conclusions

- Ethical guidelines that include the responsiveness requirement may need further elaboration
  - Possibly omit the “priorities” condition
- Despite difficulties of interpretation, the responsiveness requirement is an improvement over past research practices in which the health needs in low-resource countries were simply ignored
- Responsiveness requirement is related to the purpose of biomedical research
  - To provide health benefits to the population