Department of Ethics, Trade, Human Rights and Health Law, World Health Organization

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Dilemmas and Challenges when the North Conducts Research in the South

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Topics Addressed

I. The phenomenon of interest
II. Some fundamental ethical challenges
III. Dilemma: Standard of Care
IV. Dilemma: Post-trial obligations
   - ❖ Why is this issue so contentious?
   - ❖ What does the debate about post-trial obligations (Paragraph 30) in the 2000 Helsinki Declaration say about the revision of that document?

I. Why Does this Issue Arise?

- "10/90 Gap" (Global Forum on Health Research
  - Development of interventions targeted to poor & underserved (EDCTP/CDC)
  - Testing of existing drugs on populations for purposes of adaptation and licensing
- Drug company-sponsored tests
  - Driven by convenience and cost
  - Unable to conduct in the North

"Collaborative Research"

- Typically, sponsor (private or public) in developed country will work with investigators from developing countries
- They will collaborate with local institutions and physicians
  - May involve approval/cooperation of officials (Ministry of Health; MRC)

"Collaborative Research"

Requires:

- Institutions that are capable of collaborating (scientifically; ethically)
- Prior agreement on each party's obligations during and after research
- National rules for research within international framework
  - Ideally: national research priorities

II. Some Fundamental Ethical Issues

- Is the research truly collaborative?
  - Were investigators and institutions in the host country actually involved in identifying the topic to be investigated, designing the protocol, and interpreting the data….or merely in supplying the locale and the subjects?
  - Does the research respond to the health needs of the population and the research priorities of the host country?

II. Some Fundamental Ethical Issues

- Does the research offer a real prospect of benefit to the population from whom subjects will be drawn?
- Does the design maximize benefit/ risk ratio and minimize the risks?
  - Good scientific design
  - Appropriately trained investigators
  - Adequate precautions & compensation for injuries

II. Some Fundamental Ethical Issues

- Is the process by which subjects will be recruited appropriate and will it allow them to give—or withhold—consent voluntarily?
  - Equitable selection of subjects
  - Decision-making capacity
  - Situational (versus categorical) analysis of vulnerability (coercion or undue inducement)
  - Accurate and comprehensible information

II. Some Fundamental Ethical Issues

- What will happen at the end of the study, by way of follow-up with the study participants and with the population from which they were drawn?
  - What duties arise toward the study participants and how and by whom will they be fulfilled?
  - What arrangements are appropriate in addressing the health needs of the population?

III. Standard of Care

- Origins of the concept of "the standard of care" in medicine
- Relevance to research
  - Comparator/Placebo (especially when established treatment is not in use)
  - Care provided to research subjects who suffer harm

Origins of "Standard of Care"

- Malpractice: negligence depends on proof of departure from standard prevailing among competent practitioners in the community
  - Designed to protect patients
  - Also designed to protect physicians—patient of rural general practitioner cannot expect same level of care as from specialist/major medical center

Origins of "Standard of Care"

- Upshot: Makes what is "normative" in the descriptive or statistical sense into what is "normative" in the prescriptive or ethical sense
  - If competent practitioners do not usually use a particular method of prevention, diagnosis or treatment, then physician has not departed from due care by failing to use that method

Relevance to Research

- What care (specific intervention) is owed to participants in research—especially as the "comparator" to the intervention being evaluated?

- What care is owed to research participants as a result of injury—especially failure of prevention?

Comparator

- Issue framed by Declaration of Helsinki (2000):

"The benefits, risks, burdens and effectiveness of a new method should be tested against those of the best current prophylactic, diagnostic and therapeutic methods. This does not exclude the use of a placebo, or no treatment, in studies where no proven . . . method exists."

—Paragraph 29

Comparator

- In a setting where research subjects would otherwise have access to "the best current methods" of prevention, treatment, or diagnosis, a placebo may not be used (say, in New Haven)
- Question: Is it ethically acceptable to use a placebo in settings where the "standard of care" does NOT include "the best current methods"?

Arguments in Favor of Placebo

- May be practically (logistically) impossible to provide "the best" method used anywhere in the world
- Research question should be whether new method is better than existing
- Research participants not deprived of anything, because they would not receive the method in question if they were not in the study

Arguments Against Placebo

- Allowing use of placebo would encourage exporting research to low-resource settings (a special issue when a new method is unlikely soon to become available in that setting)
- Standard of care should be universal to avoid treating participants in resource-poor setting merely as means [for the good of others]

Compromise Position?

- Standard of care need not be "the best current method" anywhere in the world, but where sponsor shows that to be impossible, at least:
  - "an established effective intervention" (CIOMS, Guideline 11), or
  - "the best intervention available for that disease as part of the national public health system" (Nuffield Council, 7.29)

Compromise Position?

- Argument in favour of the compromise turns on the difference between "equality" and "equity"
- Treating people fairly does not require treating them exactly the same
- Unfairness could arise from risk of exploitation: presumption for single (universal) standard, but local standard allowed if justified

Care Owed to Participants

- General obligation of researchers to provide necessary healthcare services to research participants may depend on sponsorship
  - External sponsor: Presumption for standard that prevails in sponsoring country
  - Internal (and minimum for External): Local standard of care

Care Owed to Participants

- For harm arising in research (especially failure of preventive measures):

"[P]articipants who develop the disease being studied should be offered a universal standard of care....Where it is not appropriate....the minimum...that should be offered is the best available intervention as part of the national public health system for that disease." (Nuffield, 7.33)

Care Owed to Participants

- Might amount to "no care"
- Lower than standard set by UNAIDS Guidance Document (Point 16), which required "highest in host country"
- Nuffield and NBAC recommend prior agreements in place before research
- At very least, any proposal for lower standard needs special justification

Post-Trial Obligations

Why is this issue so contentious?

1. Lack of clarity about what obligations arise within the research context.
2. Many reasonable conclusions about such obligations seem too onerous.

   - This raises basic questions about the limitations on personal autonomy in situations of vulnerability.

Why Might Obligations Arise?

A. *Because of the contribution that subjects have made to the research.*

- Implies that ALL subjects in ALL research are owed continued follow-up treatment.
- "Reward" disproportionate to contribution.
- Risk of further confusing research and treatment (and creating undue inducement).
- If no promise made, why have a duty?

Why Might Obligations Arise?

B. *Because failing to continue treatment would amount to abandoning the subject.*

- Such an obligation would be limited to circumstances where the subject is

a) a patient who received

b) life-sustaining intervention in the study,

c) to which the subject lacks access by other means after the study, and

d) the discontinuation of which would cause immediate (perhaps lethal) harm.

Why Might Obligations Arise?

Conclusion:

Lack of clarity reflects unwillingness to face the impossibility of the first line of argument (too broad: everything owed to all subjects, even when no promise made) and the implications of the second line (blurs investigator-treating physician distinction)

Helsinki Paragraph 30

"At the conclusion of the study, every patient entered into the study should be assured of access to the best proven prophylactic, diagnostic and therapeutic methods identified by the study."

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"At the **conclusion of the study**, every patient entered into the study should be **assured of access** to the best proven prophylactic, diagnostic and therapeutic methods **identified by the study**."

Helsinki Paragraph 30

A. **conclusion of the study**

- When does the study “conclude”?
  - When interventions with subjects stop?
  - When scientific “conclusions” are drawn?
- What if the subject left the study (long) before it “concluded”?
  - Time at which subject left study may be when continuation of intervention was needed.

Helsinki Paragraph 30

B. assured of access

- Assured by whom: sponsor, institution, investigator? (Can they bear the burden?)
- Why impose burdens on them rather than on healthcare system?
- Access for how long? (life-long?)
- What if condition is transient?
- What if not licensed or available?

What Does the Debate on Para. 30 Say About the Document?

50 years ago, WMA undertook to state duties of physicians when they engaged in research

- Distinction from Nazi criminals
- Focus on practicing physicians (WMA not research-oriented)

What Does the Debate on Para. 30 Say About the Document?

For all the faults that have been identified, the thrust of the original Declaration of Helsinki was clear: Physicians had ethical obligations when they involved their patients in research.

What Does the Debate on Para. 30 Say About the Document?

Subsequent revisions have become more like detailed guidelines and regulations, and less like an ethical code.

"Clarification" of Paragraph 29 embodied this problem.

What Does the Debate on Para. 30 Say About the Document?

Worse problem: that WMA ends up seeming like a political body, responding to pressure.

Many see Para. 29 clarification as a concession to pharmaceutical industry (placebo rule too harsh).

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