International Research Ethics

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November 13, 2013

The views expressed are my own and do not represent any position or policy of the NIH, DHHS, or the US Public Health Service.

Overview

I. Background
II. Informed consent
III. Obligations to individuals
    A. During the trial
        i. Standard-of-care
        ii. Ancillary care
    B. After the trial
        i. Post-trial benefits
IV. Obligations to communities
    A. Responsiveness to health needs
    B. Reasonable availability of the trial intervention
    C. The Fair Benefits Framework

Background: Ethics of Multinational Research

- Multinational research is essential to understanding global health and addressing global disease burden
- Involves certain ethical issues that may be more salient and/or complex than in domestic research
- But they are not wholly unique to multinational research

Multinational collaborative research

- Research study that involves at least two countries:
  - Sponsor country pays, but research goes on in host country,

    or
  - Research is conducted at multiple sites.

Why multinational research?

- To study diseases that are more prevalent in host country, e.g. HIV prevention research
- To study health problems in host country, e.g. malaria or sleeping sickness
- To access more participants (who may be more willing to participate for health care)
- To save money

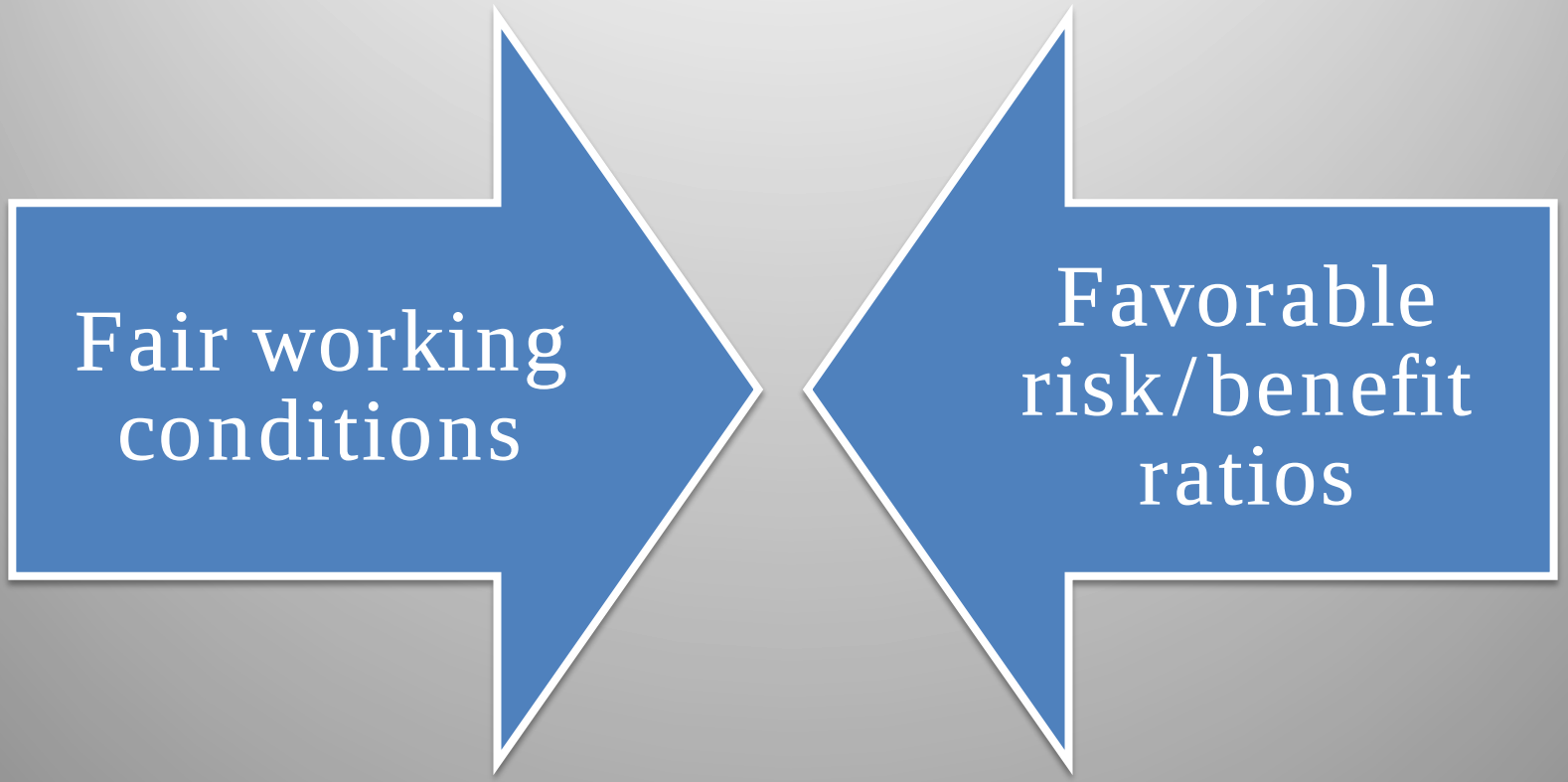
Outsourcing

- What are the ethical implications of “outsourcing”?
- Note, this is not unique to research
  - Trial of expensive blood pressure medication in India, company won’t market drug in low- or middle-income countries

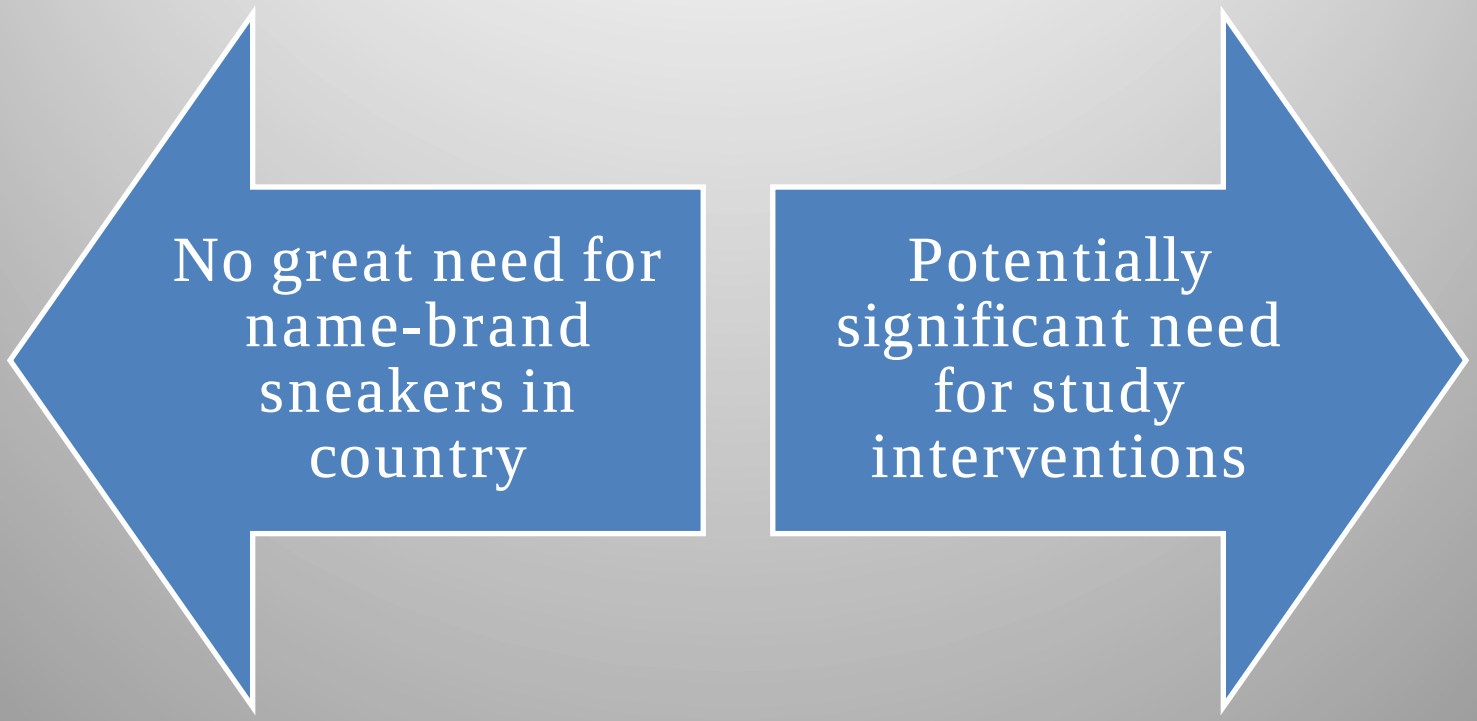
    vs

  - Sneaker factory in Indonesia, shoes will be sold in high income countries

Outsourcing



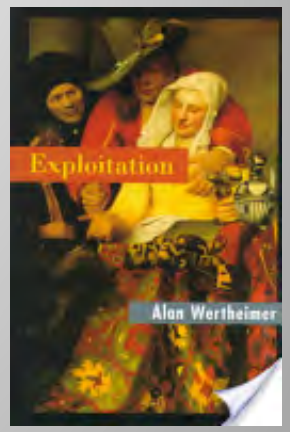
Outsourcing



Ethical concerns

- Language, cultural, and educational barriers
- Power differentials
- Exploitation
- The 10/90 gap

Exploitation of individuals



- Exploitation: benefits and burdens of a transaction are distributed unfairly
- Researchers from developed countries may be in a position to take advantage of individuals from less developed countries
- People in LMICs lack adequate health care and resources, may take on unfair risks and burdens or receive insufficient benefit

Exploitation of communities

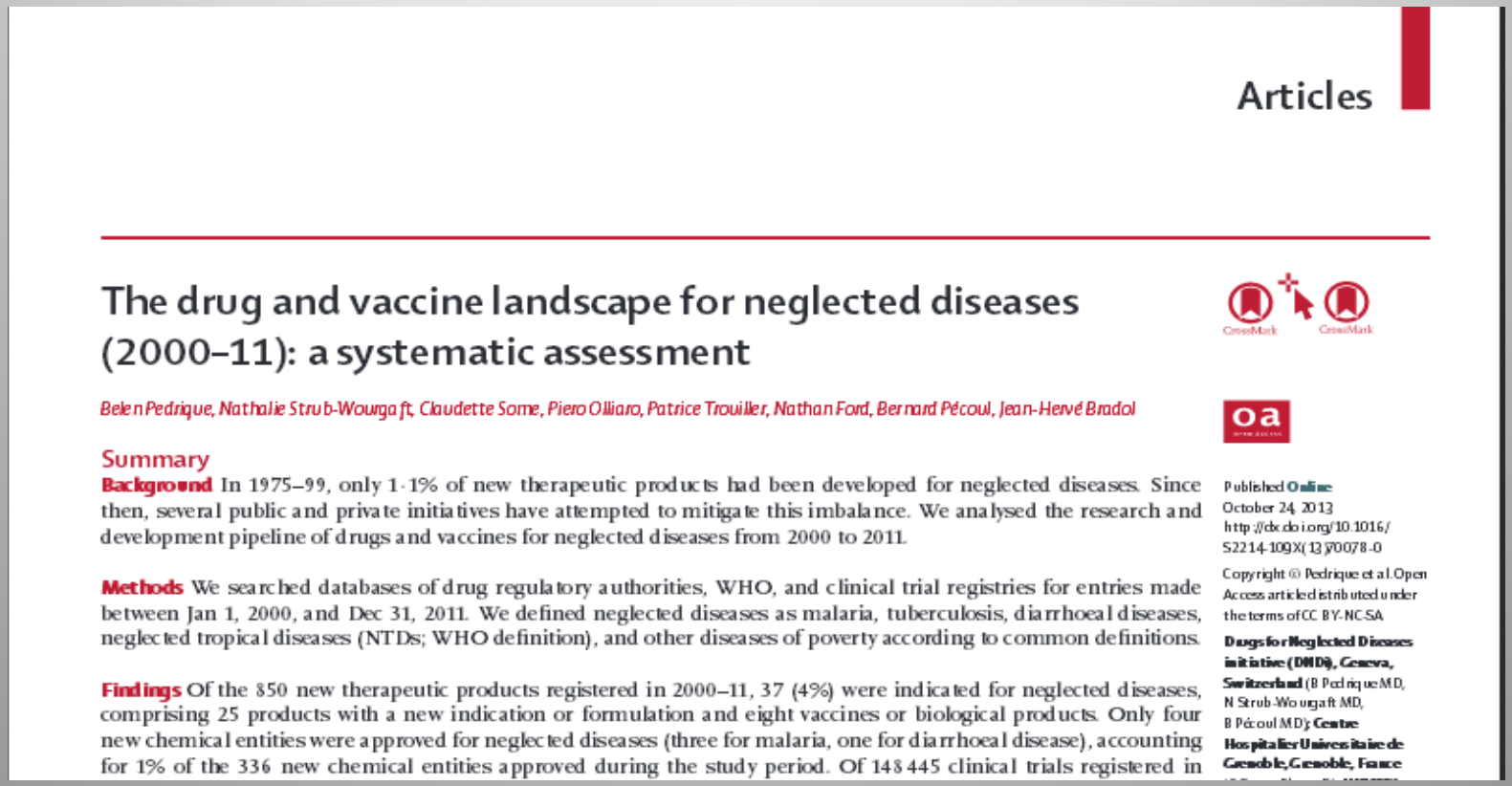
- Different from exploitation of individuals
- Resource-poor communities need benefits from research, so might agree to unfair share of the benefits and burdens
- What are the burdens of hosting research?
- What contributions do communities make that entitle them to benefits?

Current injustice related to research: The 10/90 gap

- 90% of the global funds for research related to healthcare are spent on 10% of the global disease burden

- Some claim that this figure is outdated, but evidence to the contrary

Lancet Global Health



Articles

The drug and vaccine landscape for neglected diseases (2000–11): a systematic assessment

Belen Pedrique, Nathalie Strub-Wourgaft, Claudette Some, Piero Olliaro, Patrice Trouiller, Nathan Ford, Bernard Pécoul, Jean-Hervé Bradol

Summary

Background In 1975–99, only 1·1% of new therapeutic products had been developed for neglected diseases. Since then, several public and private initiatives have attempted to mitigate this imbalance. We analysed the research and development pipeline of drugs and vaccines for neglected diseases from 2000 to 2011.

Methods We searched databases of drug regulatory authorities, WHO, and clinical trial registries for entries made between Jan 1, 2000, and Dec 31, 2011. We defined neglected diseases as malaria, tuberculosis, diarrhoeal diseases, neglected tropical diseases (NTDs; WHO definition), and other diseases of poverty according to common definitions.

Findings Of the 850 new therapeutic products registered in 2000–11, 37 (4%) were indicated for neglected diseases, comprising 25 products with a new indication or formulation and eight vaccines or biological products. Only four new chemical entities were approved for neglected diseases (three for malaria, one for diarrhoeal disease), accounting for 1% of the 336 new chemical entities approved during the study period. Of 148 445 clinical trials registered in

Published Online
October 24, 2013
http://dx.doi.org/10.1016/S2214-109X(13)70078-0

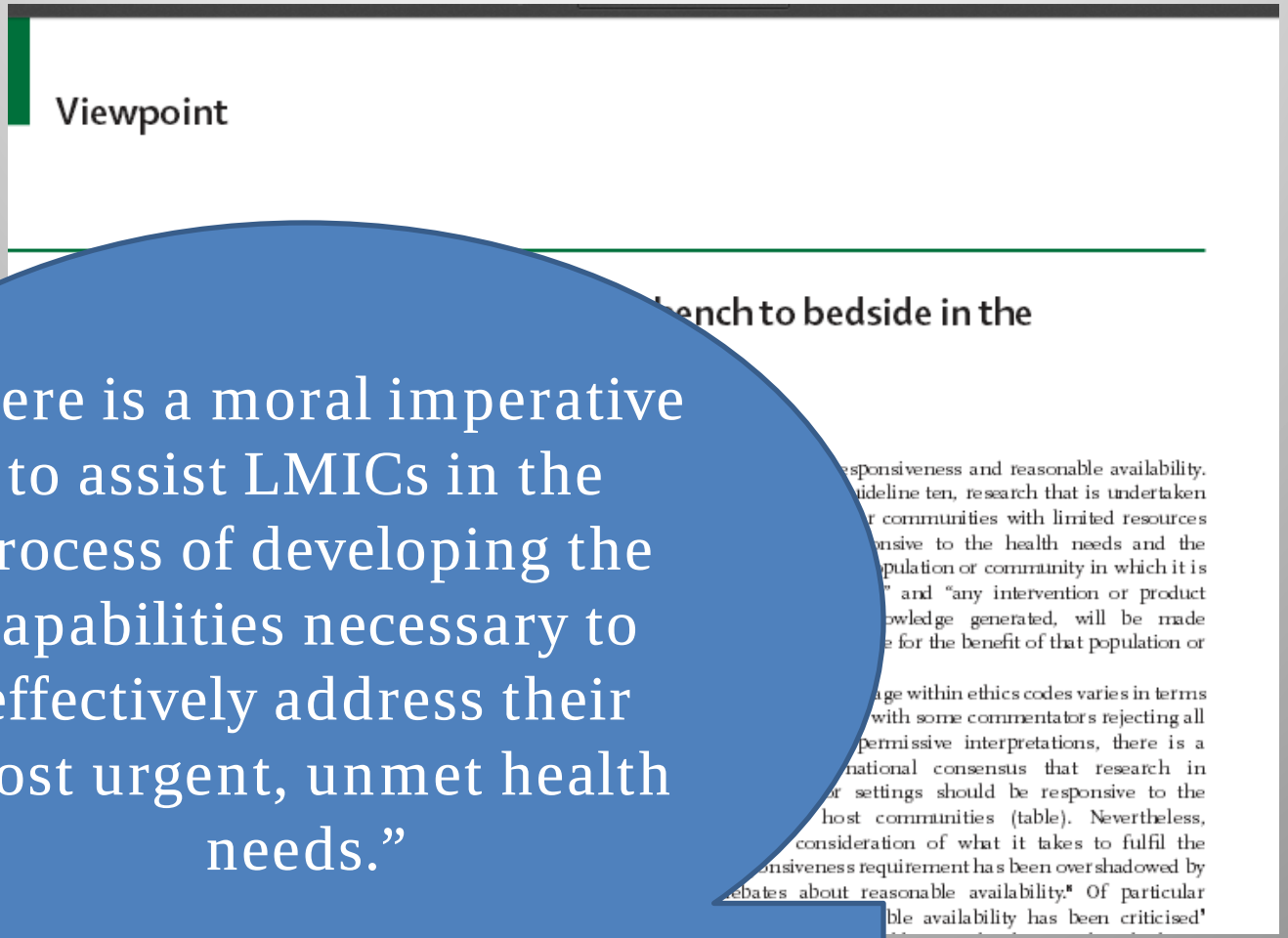
Drugs for Neglected Diseases initiative (DNDi), Geneva, Switzerland (B Pedrique MD, N Strub-Wourgaft MD, B Pécoul MD); **Centre Hospitalier Universitaire de Grenoble, Grenoble, France**

Still neglected....

- 1% of clinical trials registered in December 2011 involved neglected diseases

- Of the 850 new therapeutic products registered between 2000-11, only 4 new chemical entities were approved for neglected diseases (3 of which were for malaria)

A gap persists


Viewpoint

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esponsiveness and reasonable availability. uideline ten, research that is undertaken r communities with limited resources nsive to the health needs and the pulation or community in which it is " and "any intervention or product owledge generated, will be made e for the benefit of that population or

ge within ethics codes varies in terms with some commentators rejecting all permissive interpretations, there is a national consensus that research in r settings should be responsive to the host communities (table). Nevertheless, consideration of what it takes to fulfil the nsiveness requirement has been overshadowed by ebates about reasonable availability." Of particular ble availability has been criticised'

There is a moral imperative to assist LMICs in the process of developing the capabilities necessary to effectively address their most urgent, unmet health needs."

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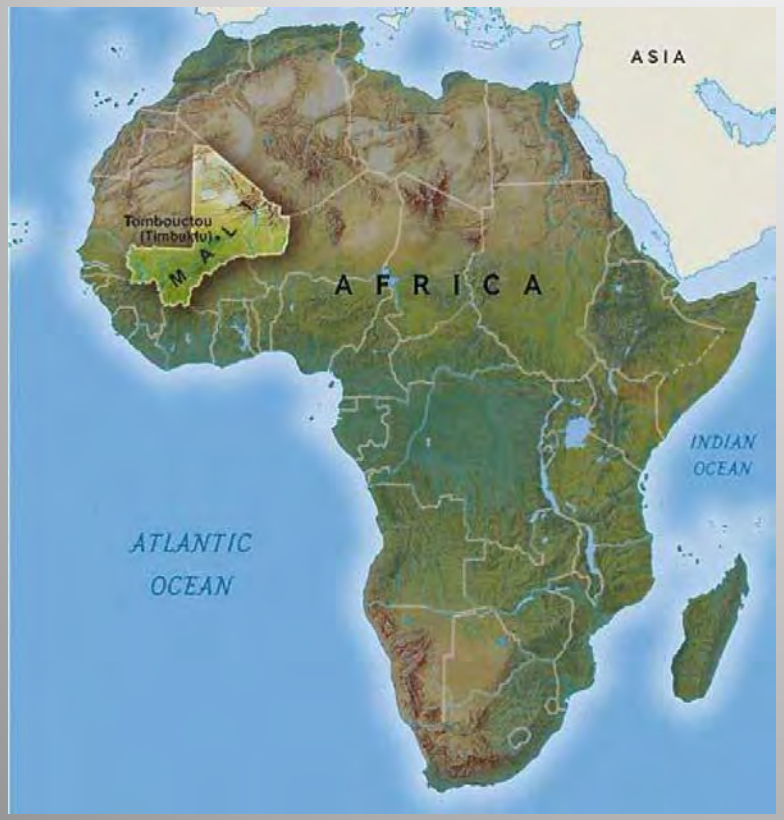
I. Informed Consent

- Obtaining informed consent in research demonstrates respect for individual autonomy
- In some cultures, individuals are understood in the context of their communities
- Some argue that in more community-centered societies, obtaining individual informed consent may lead to conflict or be disrespectful

Tiered Consent



Tiered Consent

- In a stepwise process, the researchers:
  1. Approached the leaders of the community.
  2. Conducted group discussions with the heads of extended families.
  3. Then led group discussions with mothers of children who would be involved in the study.
  4. Finally, obtained consent from individual families.
     - Also approached mothers-in-law of pregnant women before obtaining consent from the women themselves.

Tiered Consent Model: Who decides?

- Cultural claims are hard to evaluate:
  - Culture is not monolithic
  - People in power in a culture may have skewed or biased perspectives, but may control information about the culture
  - People outside a culture may not be sure how to determine whether a particular claim about a culture is true, may not know whom to ask

Empirical Data Relevant to Community Consent

One solution: Look to or gather data for the relevant community.

- In a randomized study of anti-malarial treatments in Uganda, 347 mothers giving parental consent were asked about the informed consent process.
- 94% reported making the decision about enrolling their child on their own.

Individual v. community consent

- Another model frequently used:
  - Have community discussions about the study
  - Engage with disenfranchised subgroups directly
    - Sex worker advisory boards in Vulindlela, South Africa.
  - Require individual consent for research participation (or make it very easy to withdraw)

Informed Consent in Low-literacy Populations

- In some populations, many individuals may not be able to read or sign informed consent documents
  - Signature can be an “X” or a thumbprint.
  - Researchers may need to use creative ways of disseminating information

Creative Ways of Sharing Information

- Vulindlela, South Africa
  - Community information-sharing meetings, &
  - Flip chart with pictures following a particular woman's participation
- Rakai, Uganda:
  - Giving subjects tours of the lab
  - Communicating through theater

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II. Obligations to individual subjects

During the trial:

- Standard of care/placebos
- Ancillary care

Standard of care

- What do you test a new intervention in comparison to during the trial?
  - Placebo/no intervention
  - What is locally available to most people
  - What is locally available to some
  - The best proven intervention used in the world

International guidelines

World Medical Association *Declaration of Helsinki* (2013):

"The benefits, risks, burdens and effectiveness of a new intervention must be tested against those of the best current proven intervention" with two exceptions.

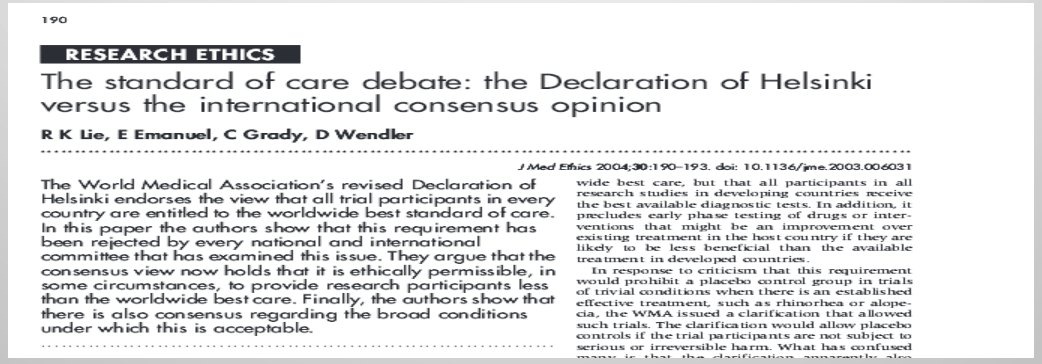
With exceptions…

- Where no current proven intervention exists; or
- Where for compelling and scientifically sound methodological reasons the use of any intervention less effective than the best proven one, the use of placebo, or no intervention is necessary to determine the efficacy or safety of an intervention and the patients…will not be subject to any risk of serious or irreversible harm. Extreme care must be taken to avoid abuse of this option.

More nuanced approaches

- Other research ethics policy documents require scientific justification for the trial design and something less than the best proven standard of care:
  - "Standard of care country endeavors to provide nationally" (UK's Nuffield Council)
  - "Highest level of care obtainable in the host country" (UNAIDS)
  - "Risks and benefits to subjects reasonably balanced, risks minimized" (NBAC)

The Declaration of Helsinki vs. other international guidelines



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RESEARCH ETHICS

The standard of care debate: the Declaration of Helsinki versus the international consensus opinion

R K Lie, E Emanuel, C Grady, D Wendler

J Med Ethics 2004;30:190–193. doi: 10.1136/jme.2003.006031

The World Medical Association's revised Declaration of Helsinki endorses the view that all trial participants in every country are entitled to the worldwide best standard of care. In this paper the authors show that this requirement has been rejected by every national and international committee that has examined this issue. They argue that the consensus view now holds that it is ethically permissible, in some circumstances, to provide research participants less than the worldwide best care. Finally, the authors show that there is also consensus regarding the broad conditions under which this is acceptable.

wide best care, but that all participants in all research studies in developing countries receive the best available diagnostic tests. In addition, it precludes early phase testing of drugs or interventions that might be an improvement over existing treatment in the host country if they are likely to be less beneficial than the available treatment in developed countries.

In response to criticism that this requirement would prohibit a placebo control group in trials of trivial conditions when there is an established effective treatment, such as rhinorrhea or alopecia, the WMA issued a clarification that allowed such trials. The clarification would allow placebo controls if the trial participants are not subject to serious or irreversible harm. What has confused many is that the clarification apparently also

- Can justify offering less than the best standard of care:
  - With sufficient benefits to the host community and
  - A favorable individual risk/benefit ratio

What is the standard of care?

- Difference between standard of care as what clinicians think is the best, and
- Standard of care that has an evidence base
- If the former, it may be important to randomize to determine whether clinicians are right
  - E.g., 41,000 patients underwent high-dose chemotherapy + autologous bone marrow transplant
  - At least 5 major RCTs showed no advantage over the alternative lower dose chemotherapy

What is the standard of care?

- For multinational research, may be different standards at different sites
- Researchers should first determine what the standard of care is at the various sites
- Next, determine that subjects are not being deprived of something proven to work that they would otherwise receive

Ancillary care

- Treatment that is provided for study participants that is NOT part of the design of the study
  - Identification of conditions that need treatment during screening and study visits
  - E.g., subjects presenting for a malaria trial who are diagnosed with parasitic diseases

Guidelines about Ancillary Care During Trials

Council for International Organizations of Medical Sciences (CIOMS):

"Although sponsors are, in general, not obliged to provide health care services beyond that which is necessary to conduct research, it is morally praiseworthy to do so."

Ancillary care in theory

- Belsky & Richardson have attempted to derive a limited obligation based on an entrustment model

Belsky L, Richardson H. Medical Researchers' Ancillary Clinical-Care Responsibilities. *BMJ* 2004;328:1494-1496.

- Others argue for ancillary care based on duty to rescue

Ancillary care in practice

- No obligation to provide ancillary care during trial in guidelines
- Many researchers do provide some amount of ancillary care, but not just to subjects—also to community members
- Very controversial, far from settled

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After the trial

- Researchers develop relationships with research subjects, who take on risks to contribute to generalizable knowledge
- When the research comes to an end, participants' need for treatment may persist
- Researchers may not want to abandon study participants altogether, or make them worse off after the research is over

Guidelines about Post-Trial Intervention Access

Declaration of Helsinki (2000):

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 that study.

Declaration of Helsinki (2008)

- At the conclusion of the study, patients entered into the study are entitled to be informed about the outcome of the study and to share any benefits that result from it, for example, access to interventions identified as beneficial in the study or to other appropriate care or benefits.

Declaration of Helsinki (2013)

- In advance of a clinical trial, researchers and host country governments should make provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial.
- This information must also be disclosed to participants during the informed consent process.

Limitations of existing guidelines

- Poorly justified
- Provide little guidance regarding long-term needs of participants
- Could create a disincentive to do research in very resource-poor settings
- Do not address uncertainty inherent in post-trial planning:
  - E.g., political changes, scientific developments

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Obligations to communities

- Research in developing countries may exploit communities by giving them an unfair share of the benefits in relation to their burdens and contributions
- As a consequence, some ethics guidelines focus on the benefits to the host community
- Open questions: What counts as a contribution? How are communities burdened by research?

Post-trial Benefits to Communities

- Two related protections to prevent exploitation of communities have been suggested:
  - Responsiveness of the research question to health needs in the host country, and
  - Reasonable availability of a successful intervention in the host country after the trial.

CIOMS: Responsiveness to Health Needs

- “Before undertaking research in a population 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....”

Responsiveness to Health Needs

- Declaration of Helsinki (2013):

  “Medical research with a vulnerable group is only justified if the research is responsive to the health needs or priorities of this group. . . .”

What is responsiveness?

- Usually easy to tell what is responsive
  - Research on HIV in sub-Saharan Africa
  - But what about an injectable drug that has to be given once a month to infants?

- Hard to tell what isn't
  - Research on baldness? Genetic advantages?

Criticisms of Responsiveness Requirement

- As long as research benefits subjects enough and does not exploit them, why does it become unethical if it is not responsive?

- If can't rule out unresponsive research, question becomes whether a study is more or less responsive than the alternatives

Criticisms of Responsiveness Requirement

- Lack of data: No way to know if this is the best policy
- May lead to undesirable outcomes for developing countries
  - It merely *prohibits* unresponsive research
  - Doesn't generate studies of neglected diseases
  - In the meantime, if there are no other options, is it better for a low income country to forbid unresponsive research?

Making sense of responsiveness

- If there are multiple studies and limited space/subjects/sites, low and middle income countries should choose among studies based on priorities

- May help identify studies that are worthy of praise and worth incentivizing

Reasonable Availability

Council for International Organizations of Medical Science (CIOMS):

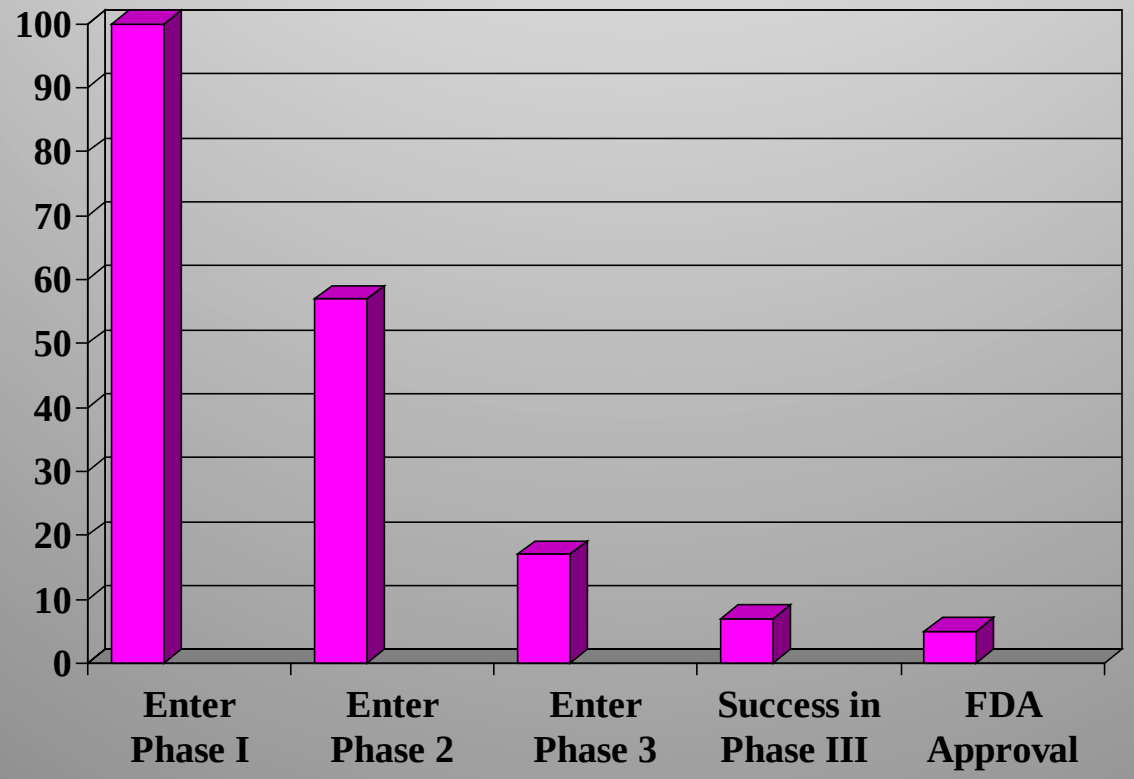
"As a general rule, the sponsoring agency should ensure that, at the completion of successful testing, any product developed will be made *reasonably available* to the inhabitants of the underdeveloped community in which the research was carried out."

Challenges to "Reasonable Availability"

- What does it mean?
  - By when should products be made available?
  - What counts as available?
- Who is the "community" receiving access?

Challenges to “Reasonable Availability”

- Sometimes requires too little



Challenges to "Reasonable Availability"

- Sometimes requires too much
  - E.g., antiretroviral trial in South Africa in the 1990s
  - Sponsor would have to purchase competitor's drug
  - Unclear what would be needed to make the drugs available

Fair Benefits Framework Proposal

- Benefits should be shared fairly amongst stakeholders, ALL potential benefits and risks need to be evaluated
  - →to research participants, during and after trial
  - → to general community, during and after trial

- Improving community risks/benefits ratio through community involvement
  - Involvement at all level of decision-making
  - Uncoerced participation
  - Transparency in decision-making

Fair Benefits criticisms

- Fair benefits framework has been criticized for requiring “too little” of researchers.
- How to identify negotiating partner?
  - Minority or disenfranchised members of the community
- Other factors may influence the distributive fairness of an outcome:
  - Disproportionately weak bargaining power of developing countries
  - Lack of available alternatives

Fair Benefits benefits

- Reasons to involve communities aside from determining how much benefit they receive:
  - Respect
  - Protection
  - Transparency
  - Buy-in

Work to be done

- May need to supplement the framework with attempts to build the bargaining power of developing countries
- Need to test how to put the framework into practice
- Need data on burdens and contributions for host commununities

Conclusions

- Ethical considerations regarding multinational research not necessarily unique
- Some concerns are more salient, pressing, or challenging in low and middle income countries
- No easy answers, but always critical to think carefully about study design, benefits and burdens for research subjects and communities
- Much work to be done to develop robust justifications and empirical bases for ethical guidance