



Scope of Post-Trial Access Issues

September 18, 2014

Mark Barnes

- 34. In advance of a clinical trial, sponsors, 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.

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.

What do we mean by “post-trial access”?



- **What period of time is required for any post-trial access?**
- **Chronic disease vs transient condition?**
- **Episode of care: treat to stabilization?**
- **Lifetime commitment, despite the natural migration of persons, families and populations?**
- **Do we think differently if the commitment is at community level vs participant level?**

Subject/participant level:

- **Continued access to the experimental agent that appears to have shown *positive results in the individual case*?**
 - **Personal preference vs. proven results?**
- **Continued access to the experimental agent that appears to have shown *positive results in the aggregate*?**
 - **Site-specific results, country-specific results or aggregate results of a multi-site study?**
- **Continued access to control arm or standard of care arm treatments?**

Subject/participant level: cross-over issues

- **Access of those on control or standard of care arm to apparently beneficial experimental agent?**
- **Access of those on experimental agent to standard of care treatment?**

Community or national level

- **If experimental agent is not further developed or if developed, is not approved for marketing?**
- **If approved, right to purchase at market price?**
- **If approved, right to purchase at discounted price?**
- **If approved, right to purchase at cost of production?**

Community or national level

- **Enhanced access to infrastructure, equipment and training left behind after the trial concludes?**
- **To prevent worsening disparities of care, improved access for a larger community, or only the community of individuals who were participants?**
- **Improved access to family clusters around participants vs a larger community?**
- **How to define a community in a polity divided by racial, ethnic, tribal and/or religious lines?**

- We will not reach conclusions.
- We will clarify that DOH paragraph 34 and similar guidelines require guidance for any practical ethical application to the complex circumstances of clinical trials.
- We will define the major issues and fault lines that may divide us, as well as identify principles of application that may be widely shared.

*The Ethics of Post-Trial
Responsibilities: History, Models,
Agreements, and Controversies*

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Disclaimer

- The views expressed are mine and should not be construed as representing those of the Department of Bioethics, National Institutes of Health, or the Department of Health and Human Services.
- I have no conflicts of interest to declare

Researchers' Responsibilities

Ask a valuable research question



Develop a research proposal



Minimize Risk and maximize benefit



Seek independent review & approval



Obtain informed consent



Monitor, respect confidentiality, etc.



?? Post Trial ??

Post-trial responsibilities- History

- Most guidance silent (until the 1990s) on what should happen at the end of a trial. Prevailing view/practice was that obligations ended with the trial.
- What changed?
 - Increased volume of international research
 - HIV research
 - Research in communities with limited access to health care
 - Concerns about exploitation

International research

- Minimizing exploitation in international collaborative research
 - Responsiveness to host needs/priorities
 - Community benefits, including reasonable availability of products developed
 - Capacity Building
 - Collaboration and community involvement

CIOMS, Helsinki, NBAC, Nuffield Council and others

History

- Commentary to guideline 15: Obligations of sponsoring and host countries.(CIOMS 1993)

“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 inhabitants of the underdeveloped community in which the research was carried out.”

History

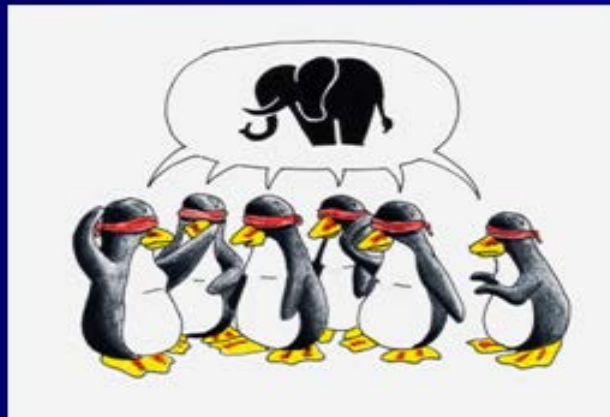
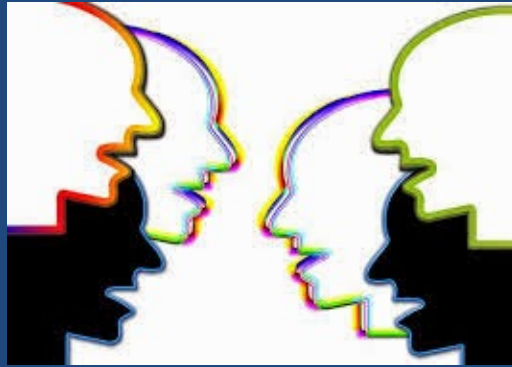
“Unless the interventions being tested will actually be made available to the impoverished populations that are being used as research subjects, developed countries are simply exploiting them in order to quickly use the knowledge gain from the clinical trials for the developed countries own benefit.”

AnnasG,GroдинM.Am J Public Health1998

Post-trial access: Data

Who should be guaranteed IL-2 treatment, if proven effective, after the trial?

<i>Participants</i>	<i>IRB/REC</i>	<i>Investigators</i>
•Participants	7%	26%
•HIV-infected people in your country who need it	7%	13%
34%	26%	
•Every HIV-infected person in the world who needs it	83%	
	29%	42%
•No one	2%	10%
		19%



Selected Post trial responsibilities of investigators/sponsors

- To participants
 - Compensation for injury
 - Continued access to beneficial interventions (investigational or otherwise)
 - Transition
- To the community
 - Continued partnerships
 - Infrastructure and training
 - Access to products or to other benefits of research
- To society (including participants and communities)
 - Access to and integration of resulting knowledge

HIV treatment trial in South Africa

- Pharmaceutical company proposes treatment trial of a new promising combination of antiretroviral medications
- Ethics committee disapproves requiring access to the ART combination for those who benefit for as long as they benefit
- Company not willing- too costly, partly because they have to buy rival company drugs and the commitment is open-ended

•Community activists argue that ART during the

History

- “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.*”
 - Declaration of Helsinki #30, WMA 2000

History of Guidance re: Post trial responsibilities to Participants

Year	Authority	Language used
2000	WMA Declaration of Helsinki	At conclusion, every person should be “assured of access” to best proven intervention identified by the study
2001	U.S. National Bioethics Advisory Committee*	Researchers and sponsors should make good faith efforts to “secure...continued access” to needed interventions that have been proven effective...Protocols should describe duration, extent and financing of such continued access or justify ...”
2002	CIOMS*	Sponsor should “continue to provide” access to beneficial intervention...pending its approval by a drug regulatory agency.
2002	Nuffield Council on Bioethics	“...researchers should endeavor before initiation of a trial to secure post-trial access for effective interventions for participants... and justify lack of such agreements
2004	The Wellcome Trust*	..although funding post-trial access is outside their remit, “[t]he Wellcome Trust may consider it an ethical requirement to guarantee post-research access to treatments to participants involved in research investigating chronic or progressive conditions.”

History of Guidance re: Post trial responsibilities to Participants

Year	Authority	Language used
2004	WMA Helsinki (clarification)	Necessary during study planning process to “identify” post-trial access to beneficial interventions or other appropriate care... Must be described in study protocol for review by ethical review committee
2005	National Institutes of Health*	For antiretroviral treatment trials conducted in developing countries, the NIH expects investigators/contractors to address the provision of antiretroviral treatment to trial participants after trial completion
2005	Nuffield Council on Bioethics*	“It is essential [for stakeholders] to begin negotiations about post-trial treatment at an early stage when planning research.” However, “requir[ing] researchers or sponsors to fund the provision of interventions once the research is complete may be unrealistic and lead to sponsors curtailing other research.”
2008	WMA Declaration of Helsinki (revision)	Research protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits. Participants should be “informed” about the study outcome, “entitled” to share in benefits.
2013	WMA Declaration of Helsinki (revision)	In advance of a clinical trial, sponsors, 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.

Evolution of Guidance

Access

“Assured”
“Secured”
“Provided”



“Identified”
“Addressed”
“Described”
“Make provisions”

To:

“Best proven identified by
study”
“Needed and
proven effective”
“Shown to be beneficial”



“Beneficial”
“Other appropriate care
and benefits”
“identified as beneficial”

By:

“Sponsor”
NS



“Addressed by
investigator”
“Reviewed by IRB/REC”
“Sponsor, researcher,
and host country gov’t”

Areas of Agreement

- Investigators have some post –trial responsibilities to participants
- Which likely include:
 - Planning in advance about what will happen at the end of the trial (reasonable efforts to help participants access beneficial treatments that are still needed)
 - Describing plan to review committees and also to participants
 - Informing participants about study outcomes
 - Honoring commitments

Areas of Agreement

- Individuals (including research participants) should continue to receive treatment or care that they need
- Investigators are doing what they can, and sometimes are very creative

Post-trial benefits to participants

- Creative solutions: HIV-NAT drug fund
- “Although we stated clearly in the consent form that we could not promise post-trial drug supply, we were compelled to take action when faced with the tragic prospect of watching patients reverse their excellent quality of life gained while on antiretrovirals.”

—Ananworanich et al. Lancet 2004; 364:101-2.

Unsettled areas

- What is the *scope* and the *limit* of investigator post-trial responsibilities to participants?
 - Extent of the responsibility - ensuring access to needed treatment? Transition?
 - Access to study treatments or other treatments, ancillary care, etc?
 - Duration of responsibility?
 - Financial responsibility?
 - Basis of the responsibility?

Unsettled areas: Basis or justification

- Exploitation
- Needs of participants, avoiding harm
- Reciprocity
- Duty of rescue
- Global justice
- Researcher- participant relationship

NBAC *Ethical and Policy Issues in International Research*, 2001; Millum J. *Bioethics* 2011; Sofar N, Strech D. *Public Health Ethics* 2011; others

Unsettled areas: reasons that argue against or limit an obligation

- Research \neq health care
- Researchers/sponsors not in a position
- Disincentive, costs, logistical complexity
- Participants consent
- Undue influence and therapeutic misconception
- Disadvantaging others
- Legal challenges



Minimize Exploitation

- Taking “unfair” advantage
- Increase benefits to participants by continuing access after the trial.
- Minimize exploitation of individual research participants by offering them an acceptable or favorable risk/benefit balance, and obtaining their voluntary and informed consent. Are participants exploited if they consent to participation without PTA?
- Paradox: Should those participants who did not benefit (and bore burdens) have a stronger claim to benefits at the end of a trial?

Needs of participants and avoiding harm

- Ongoing medical need (esp. chronic illness)
- May be beneficial to continue medication or treatment, may be harmful to withdraw

“If a patient is still sick, how will you stop the drugs?” Shaffer D et al. JME 2006

- BUT- Goal of research is not to “treat” patients. Research is different than health care, researchers may not have the authority or resources to provide ongoing health care

Reciprocity

- Participants contribute to the research goals and accept risks
- Recognition of and compensation for contributions
 - “If I’m going through the study, and I’m putting my butt on the line, they should take care of me down the line” (Sofaer et al. 2009)
- BUT- Other ways to reciprocate
- Giving priority to research participants may disadvantage others

Duty of rescue

- Duty to rescue those in need
- Benefit to person rescued and risk/cost to rescuer
- Short term versus long term
- Research participants versus others in need?
- Researchers versus others?

Global justice

- Opportunity to address background disparities, including access to care
- Why researchers more than others (e.g. governments or international aid organizations)?
- Research participants versus others in need?
- Making treatments, knowledge, or other benefits widely available may do more to correct injustice than continuing to treat participants

Researcher- participant relationship

- Similar to physician/patient?
- Patient needs and expectations
- Exacerbate a therapeutic misconception?
- Responsible ending of relationships



Post trial responsibilities to participants

- Some intuitively powerful justifications for some researcher obligations
- Yet, incomplete justification as they fail to explain some widely held intuitions, may apply in only certain cases, and are not specific to an obligation to provide participants with continued post-trial access to treatment
- There are important arguments against such an obligation

Unsettled areas

- What counts as a reasonable plan or effort?
 - Providing treatment for as long as needed
 - Negotiating with local health authorities, or with pharmaceutical company for continued access
 - Transferring back to care provider
 - Referring to usual health care
 - Informing about options for treatment
 - Extending availability of treatment for a defined period of time
 - Access until licensed

Unsettled areas

- How should circumstances be considered in assessing the reasonableness of the plan?
- What counts as a legitimate justification, if any, for no plan?
- Should (how should) the lack of a plan affect the acceptability of the study?

Unsettled areas

- What particular responsibilities should investigator/sponsors have that others (host governments, local health officials, healthcare providers, NGOs international organizations, others) do not have?
- Does it matter how well resourced the researcher or sponsor is?
- How should decisions about sharing responsibility and dividing up responsibilities be made?

Unsettled areas

- How should the researcher/sponsor understand and divide post-trial responsibilities (and resources)
 - To participants
 - To the larger community
 - To further research

Unsettled areas

- Should research participants have priority over other citizens for treatment or care?
- Are there circumstances that shift their priority? Or increase the obligation to provide research participants with treatment/care?

- Clinical research aims to find new knowledge to improve health and health care.
- Participants in clinical research contribute invaluablely to this goal.
- Earnest effort should be made to find ways for participants who need care and treatment at the end of a clinical trial to receive it.

WMA Declaration of Helsinki

Process and Perspectives



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Outline

- History and background of the WMA and the Declaration of Helsinki
- History and evolution of the DoH's stance on post-trial obligations
- Interpretation and expectations of Paragraph 34

History and background of the WMA and the Declaration of Helsinki

- The World Medical Association (WMA) is an international organization representing the physicians of the world
- It was founded on September 17 1947, when physicians from 27 different countries met at the First General Assembly of the WMA in Paris

- The WMA was created to ensure the independence of physicians, and to work for the **highest possible standards of ethical behaviour and care by physicians**
- This was particularly important to physicians after the atrocities of WWII, and therefore the WMA has always been an independent confederation of free professional associations
- Funding has been by the annual contributions of its members, which has now grown to 106 National Medical Associations

- As an organization promoting the highest possible standards of medical ethics, the WMA provides ethical guidance to physicians through its Declarations, Resolutions and Statements. These also help to guide National Medical Associations, governments and international organizations throughout the world.
- The International Code of Medical Ethics was published by the WMA in 1948 and was followed by the Geneva Declaration in 1949.

- Shortly after its foundation, the WMA initiated discussions on ethical recommendations for medical research
- A first proposal was submitted to the Medical Ethics Committee in 1953
- A Resolution on Human Experimentation was subsequently published in 1954
- The first draft of the DoH was presented by the Committee in 1961

- After 3 years of debate, the 18th General Assembly of the WMA adopted the first DoH setting out “recommendations guiding doctors in clinical research” in Helsinki in 1964
- It was the first document of its kind at the international level, though the Nuremburg Code (1947) also addressed some of the same issues



WMA Declaration of Helsinki - Ethical Principles for Medical Research Involving Human Subjects

Adopted by the 18th WMA General Assembly, Helsinki, Finland, June 1964, and amended by the:

- 29th WMA General Assembly, Tokyo, Japan, October 1975
- 35th WMA General Assembly, Venice, Italy, October 1983
- 41st WMA General Assembly, Hong Kong, September 1989
- 48th WMA General Assembly, Somerset West, Republic of South Africa, October 1996
- 52nd WMA General Assembly, Edinburgh, Scotland, October 2000
- 53th WMA General Assembly, Washington 2002 (Note of Clarification on paragraph 29 added)
- 55th WMA General Assembly, Tokyo 2004 (Note of Clarification on Paragraph 30 added)
- 59th WMA General Assembly, Seoul, October 2008
- 64th WMA General Assembly, Fortaleza, October 2013

- Since the 2000 version, revisions have included a public discussion and consultation process
- The 2013 revision process lasted two years and included 2 meetings on placebo controls (Sao Paulo), 3 formal stakeholder consultation meetings (Capetown, Tokyo, Washington), input from the bioethics community (Rotterdam) and dozens of written submissions
- The Working Group (Japan, Brazil, Uruguay, USA, Germany and Denmark; advisors and observers from Canada, South Africa, Uganda, Norway and Finland) met regularly over the two year period
- The final version was approved at the General Assembly meeting in Fortaleza in October 2013

- During the consultation process for the 2013 revision, there was near complete consensus about the need to clarify the DoH's position on post-trial access
- However, there were significant differences with respect to the level of detail that commenters felt should be included



History and evolution of the DoH's stance on post-trial obligations

- First reference to post-trial access is in the 2000 revision
- Primarily a result of HIV trials in Africa, as well as general agreement that the principle of justice was applicable to research ethics as well as to bioethics more broadly
- Significant controversy with negative feedback from industry, the FDA and CIOMS, among others, leading to 2004 note of clarification

HIV clinical trials

- The AIDS Clinical Trials Group (ACTG) Study of Zidovudine in maternal-infant transmission of HIV had been published in 1994
- This was a placebo controlled trial which showed a reduction of nearly 70% in the risk of transmission, and Zidovudine became a de facto standard of care
- It was subsequently learned that patients in trials in the US had essentially unrestricted post-trial access to the drug, while those in developing countries did not



2000 revision

- New 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.

2004 revision – note of clarification

- Note of clarification on paragraph 30 of the WMA Declaration of Helsinki: The WMA hereby reaffirms its position that it is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care must be described in the study protocol so the ethical review committee may consider such arrangements during its review.

- 2000 version: 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.



- 2004 clarification: The WMA hereby reaffirms its position that it is necessary during the study planning process **to identify post-trial access** by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care. Post-trial access arrangements or other care **must be described in the study protocol** so the ethical review committee may consider such arrangements during its review.

2008 revision

- Paragraph 14: The design and performance of each research study involving human subjects must be clearly described in a **research protocol**. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, other potential conflicts of interest, incentives for subjects and provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. **The protocol should describe arrangements for post-study access by study subjects to interventions identified as beneficial in the study or access to other appropriate care or benefits.**

- Paragraph 33: 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.**

2013 revision



- Paragraph 22:
- The design and performance of each research study involving human subjects must be clearly described and justified in a **research protocol**. The protocol should contain a statement of the ethical considerations involved and should indicate how the principles in this Declaration have been addressed. The protocol should include information regarding funding, sponsors, institutional affiliations, potential conflicts of interest, incentives for subjects and information regarding provisions for treating and/or compensating subjects who are harmed as a consequence of participation in the research study. **In clinical trials, the protocol must also describe appropriate arrangements for post-trial provisions.**

- **Post-Trial Provisions**
- Paragraph 34: In advance of a clinical trial, sponsors, 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.

- 2008 Paragraph 33: 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.



- 2013 Paragraph 34: In advance of a clinical trial, sponsors, 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.

- 2000 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.
- 
- 2004 Note of clarification : It is necessary during the study planning process to identify post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care.
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- 2013 Paragraph 34: In advance of a clinical trial, sponsors, 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.

Interpretation and expectations of Paragraph 34

- Including the issue of post-trial access in the DoH since the 2000 revision has always been controversial
- Paragraph 34 of the 2013 version names the parties to be involved (sponsors, researchers and host country governments) and links the obligation to the ongoing needs of the participants
- It strengthens the requirement to provide post trial access compared to the 2008 version (though still “should” and not “must”)

Because the DoH is intended as a declaration of ethical principles, it may never be in a position to address and clarify all of the complex details around post-trial access

Other ongoing concerns/questions

- What to do in the delay between closure of a trial and analysis of the findings?
- Who **exactly** is responsible for providing the benefits?
- What kind of benefits need to be provided? For whom? For how long?
- Is the claim is more valid when no alternative effective treatment exists?
- Whether such arrangements are a disincentive to researchers

Morris K. Revising the Declaration of Helsinki. The Lancet, June 2013.

- The issue of post-trial access needs more ongoing discussion and thought. A key question is who is responsible for what? We need to get this right, by thinking about who can reasonably be held responsible and how to exert those responsibilities between sponsors of trials, individual researchers, governments, and health systems.
- It's important to address beforehand the arrangements surrounding closure of a trial. But if research is responsive and welcomed by a community, and consent for participation is truly informed and given freely, what is the ethical basis for further moral obligations?



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The Council for International Organizations of Medical Sciences (CIOMS) Approach

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Disclosure

- I. Member of the Working Group on the Revision of CIOMS 2002 International Ethical Guidelines for Biomedical Research Involving Human Subjects.
- II. Expert commentator at three World Medical Association meetings on 2013 revision to the Declaration of Helsinki.
- III. Views expressed in this presentation are entirely my own.

Origins

- I. Late 1970s CIOMS, in cooperation with WHO, prepared guidelines:
“to indicate how the ethical principles that should guide the conduct of biomedical research involving human subjects, as set forth in the Declaration of Helsinki, could be effectively applied, particularly in developing countries, given their socioeconomic circumstances, laws and regulations, and executive and administrative arrangements”
(CIOMS 2002 p.7).

Origins

- I. Guidelines issued in 1982, 1993, and 2002.
- II. Guidelines are currently under revision.
 - A. Relationship to the Declaration of Helsinki is evolving.
 - B. Retain special focus on:
 - 1. International collaborative research.
 - 2. Research in low-resource countries.

Key Questions

- I. Rationale for post-trial responsibilities?
- II. What are the “objects” of post-trial claims?
- III. Who are the “recipients” of post trial responsibilities?
- IV. Who are the “agents” with post-trial responsibilities?
- V. What are the limits of post-trial responsibilities?

Guideline 10: Research in populations and communities with limited resources

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.

I. Rationale

“If the knowledge gained from the research in [countries where governments lack the resources to make such products or benefits widely available] is used primarily for the benefit of populations that can afford the tested product, the research may rightly be characterized as exploitative and, therefore, unethical.” (Guideline 10, p. 52).

I. Rationale

General Ethical Principles: Justice

- “In general, the research project should leave low-resource countries or communities better off than previously or, at least, no worse off. It should be responsive to their health needs and priorities in that any product developed is made reasonably available to them, and as far as possible leave the population in a better position to obtain effective health care and protect its own health” (p. 18).

I. Rationale

Interpretation: Division of labor between research and health systems.

- In low-resource settings special care is required to maximize the likelihood that host communities will benefit from new knowledge and interventions.
- Research should develop knowledge and interventions that are relevant to host community health needs and are likely to expand the capacity of local health systems to meet those needs.

II. “Objects” of Post-Trial Concern

- A. New knowledge relevant to health needs
- “...when the outcome is scientific knowledge rather than a commercial product...there must be assurance...that the scientific knowledge developed will be used for the benefit of the population” (Guideline 10, p. 53).
 - “This should not be construed as precluding studies designed to evaluate novel therapeutic concepts...” (p. 53).
 - “If the concept is found to be valid, subsequent phases of the research could result in a product that could be made reasonably available at its conclusion” (p. 53).

II. "Objects" of Post-Trial Concern

B. Infrastructure

- “The development of a health-care infrastructure should be facilitated at the onset so that it can be of use during and beyond the conduct of the research.” (Guideline 10, p. 52)

C. Vindicated interventions

- “Additionally, if an investigational drug has been shown to be beneficial, the sponsor should continue to provide it to the subjects after the conclusion of the study, and pending its approval by a drug regulatory authority” (Guideline 10 p.52).

II. "Objects" of Post-Trial Concern

D. Care and compensation for harms.

- “Investigators should ensure that research subjects who suffer injury as a result of their participation are entitled to free medical treatment for such injury and to such financial or other assistance as would compensate them equitably for any resultant impairment, disability or handicap. In the case of death as a result of their participation, their dependents are entitled to compensation. Subjects must not be asked to waive the right to compensation” (Guideline 19: Right of injured subjects to treatment and compensation).

II. “Objects” of Post-Trial Concern

E. Supporting health services

“External sponsors are ethically obliged to ensure the availability of:

- ...services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed as a result of the research reasonably available to the population or community concerned.” (Guideline 21: Ethical obligation of external sponsors to provide health-care services)

II. “Objects” of Post-Trial Concern

F. Research-related capacity building.

- “External sponsors and investigators have an ethical obligation to contribute to a host country’s sustainable capacity for independent scientific and ethical review and biomedical research.” (Guideline 20 p. 80).
- “The amount of capacity building reasonably expected should be proportional to the magnitude of the research project” (p. 80).

III. “Recipients” of Post-Trial Concern

A. Host countries & host communities

1. New knowledge relevant to health needs
2. Improved infrastructure
 - i. Access to new modalities (after approval).
 - ii. Capacity for research-related activities.

III. “Recipients” of Post-Trial Concern

B. Study Participants

1. Vindicated modalities (from study conclusion until approval).
2. New knowledge:
 - “...after the completion of the study, subjects will be informed of the findings of the research in general, and individual subjects will be informed of any finding that relates to their particular health status” (Guideline 5 p. 38)

IV. Agents with Post-Trial Responsibilities?

A. Study sponsors & researchers:

1. Negotiate post-trial availability with “representatives of stakeholders in the host country” (p. 52)
 - “national government, the health ministry, local health authorities, and concerned scientific and ethics groups, as well as representatives of the communities from which subjects are drawn and non-governmental organizations such as health advocacy groups” (p. 52).
2. Ensure availability of care for injured.
3. Ensure availability of supporting health care services. (Guideline 21)

V. Limits of Post Trial Obligations

- A. Pre-trial planning for responsiveness.
- B. Negotiation with stakeholders for infrastructure improvements and reasonable availability.
 1. Pricing / licensing
 2. Funding commitments

V. Limits of Post Trial Obligations

C. Transitional responsibilities

1. Access for study subjects to beneficial investigational modalities.
2. Access to “services that are a necessary part of the commitment of a sponsor to make a beneficial intervention or product developed as a result of the research reasonably available to the population or community concerned.”
3. Transitional responsibilities appear to end once product is reasonably available.

V. Limits of Post Trial Obligations

D. Ancillary Care?

- “Although sponsors are, in general, not obliged to provide health-care services beyond that which is necessary for the conduct of the research, it is morally praiseworthy to do so.” (Guideline 21, p. 82).
- “When prospective or actual subjects are found to have diseases unrelated to the research, or cannot be enrolled in a study because they do not meet the health criteria, investigators should, as appropriate, advise them to obtain, or refer them for, medical care.”

Conclusion

- I. CIOMS views provision of health care as the responsibility of the local health system.
- II. Function of research is to generate information and interventions that will improve those systems.
- III. Post-trial responsibilities focus primarily on ensuring:
 - A. Availability of knowledge and interventions relevant host population needs.
 - B. Care and compensation for injuries.
 - C. Continuity of care for participants who benefit from investigational agents.

Post-trial Obligations: Policy Approaches Around the Globe

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The opinions expressed are my own. They do not reflect any position or policy of the U.S. Government or the NIH.

Overview

- International regulations
- Funders' policies
- Regulations vs. ethical guidance
- Data on what happens in practice

International regulations

Categories of regulatory approaches to post-trial access

Requirement: Researchers/ sponsors should	Representative countries
Provide	
Ensure	
Refer	
Describe	
[Silence]	

More



Less

Categories of regulatory approaches to post-trial access

Requirement: Researchers/sponsors should	Representative countries
Provide	?
Ensure	Brazil, Canada, Nepal, Japan, Cameroon
Refer	Philippines
Describe	India, Council of Europe, New Zealand, Nigeria, South Africa, Australia
[Silence]	U.S.

More



Less

Caveats

- Canada: depends on phase of research, whether treatment is beneficial and safe
- Japan: should “make an effort to ensure”
- Nepal: depends on nature of disease, trial, interventions
- Brazil: must prove superiority over standard treatment
- India: indirect community benefit may suffice; small studies need not comply

Examples

Ensure

Brazil

For drug experiments: “access to the medicine being tested must be assured by the sponsor or, if there is no sponsor, by the institution, researcher, or promoter in the event that its superiority over the conventional treatment is proven.”

Resolution 251/1997

Japan

“Even after completion of the clinical study, the principal investigator should make an effort to ensure that the subjects have access to the best preventive, diagnostic, and therapeutic methods identified by the clinical study concerned.”

Ministry of Health, Labor, and Welfare guidelines (2008)

Canada's Tri-Council Policy Statement (2nd ed.) 2010

- **Trials involving pharmaceutical products:**
 - Phase I: no requirements for post-trial access
 - Phase II: Researchers shall “make reasonable efforts to secure continued access...for those patients for whom the drugs appear to be efficacious.”

<http://www.pre.ethics.gc.ca/eng/policy-politique/initiatives/tcps2-eptc2/chapter11-chapitre11/>

Canada's TCPS

- Trials involving pharmaceutical products:
 - Phase III: “Researchers and the REB should also address the issue of continuing access to the experimental therapy after the trial closes. If the treatment benefits participants and is safe, the proposal should state whether it will continue to be provided....REBs should be concerned about what provisions are possible to ensure that participants continue to receive adequate treatment.”

Refer

Philippines

- “The protocol must include provisions for aftercare, including closure activities and a proper referral mechanism to deal with the health needs of participants and members of the research team.”

National Ethical Guidelines for Health Research (2006),
https://webapps.sph.harvard.edu/live/gremap/files/ph_natl_ethical_gdlns.pdf.

Describe

India

- Favorably cites 2004 Declaration of Helsinki as follows:
 - Identify and describe in protocol “post-trial access by study participants to prophylactic, diagnostic and therapeutic procedures identified as beneficial in the study or access to other appropriate care....”
- Adds exceptions: Indirect community benefit, small scale/student projects

Nigeria

- “Comprehensive delineation of risks and benefits should be done for participants during the research, the population hosting the research and for both participants and population after completion of research...”

http://www.nhrec.net/nhrec/NCHRE_10.pdf

Silence

U.S. Regulations

[Intentionally left blank]

Post-trial access to information

- Canada, Nigeria, New Zealand, South Africa, Council of Europe require plans to distribute information and research results to participants and communities
- Studies conducted in Rwanda also have to be published in Rwanda

Funders' Policies

Funders' policies

- U.K. Wellcome Trust: funding post-trial provisions outside remit to support research
- May nevertheless take post-trial provisions into account when deciding whether to award grants
- And may require post-trial access for chronic or progressive conditions

Funding policies

- French Agence Nationale de Recherche sur le Sida et le Hépatites Virales (ANRS) restricts HIV prevention research to areas where public ART programs exist
- Presumably to ensure post-trial access

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NIH Guidance

NIH Guidance (March 2005): “For antiretroviral treatment trials conducted in developing countries, the NIH expects investigators/contractors to address the provision of antiretroviral treatment to trial participants after their completion of the trial.”

<http://grants.nih.gov/grants/policy/antiretroviral/>

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NIH Guidance

- However, the Guidance document notes that “NIH’s authority to ‘encourage and support research’ does not extend to providing treatment following the completion of that research. 42 USC 284(b)(1)(A).”
- Therefore, the NIH recommends “investigators/contractors work with host countries’ authorities and other stakeholders to identify available sources of antiretroviral treatment.”

Concern about diversion effects

- Policies could divert beneficial research to places where infrastructure already exists and away from some of the worst-off
- See Lynch HF, Dawson L, Adding insult to injury: reluctance to engage in clinical research with at-risk groups further disenfranchises these populations, *Am J Bioeth* (2009).

**How do regulations & policies
compare to ethical guidance?**

Ethical guidance

Year	Issuing Authority	Target	Nature of Obligation
2001	U.S. National Bioethics Advisory Committee	Researchers and sponsors	Good faith efforts to “secure” post-trial access to beneficial interventions
2002	CIOMS	Sponsors	“Continue to provide” access to beneficial intervention pending regulatory approval.
2005	Nuffield Council on Bioethics	Stakeholders	“Begin negotiations about post-trial treatment at an early stage.” Requiring researchers/sponsors to fund treatment “may be unrealistic and lead to sponsors curtailing other research.”
2012	UNAIDS Ethical considerations in biomedical HIV prevention trials	Stakeholders	Participants who are infected during a prevention trial should “be provided access to treatment.”
2013	WMA Declaration of Helsinki	Stakeholders (Sponsors, researchers, host-country governments)	“[M]ake provisions for post-trial access for all participants who still need an intervention identified as beneficial in the trial.”

Regulations vs. ethical guidance

- **Some similarities**
 - No clear consensus
 - Plan in advance, inform participants
 - Important that intervention is beneficial
- **Some differences**
 - No regulations seem to require provision, more caveats/nuance in some regulations
 - Ethics guidance tends to be more stringent, but recognizes more stakeholders

What is happening in practice?

Empirical data

- Few guarantees to provide care after a study is over
- Focus on short-term provision, transitioning participants to other sources of care
- S. Shah, S. Elmer, C. Grady, American Journal of Public Health (September 2009).
- Ciaranello A, Walensky RP, Sax PE, Chang Y, Freedberg KA, Weissman JS., HIV Clinical Trials (Jan./Feb. 2009).

Study of implementation of NIH guidance

- All researchers and sponsors addressed post-trial obligations
- 1 study: participants could buy drugs at a clinic for U.S.\$30-150/month.
- Most studies focused on referral
- Some provided ART short-term, including up to commercial availability

Need for more empirical data

- Existing data focus on post-trial plans
- Need data on:
 - How well are plans implemented?
 - What are barriers to successful transitions?
 - How are barriers to access being overcome?
 - Are control groups given post-trial access?

Summary

- Regulations tend to focus on ensuring or describing options for post-trial access
- Closer to consensus on sharing information and results post-trial
- Stronger obligations in some ethics guidance and funders' policies, but apply to more stakeholders
- In practice, researchers focus on referral

South African Regulations

- MRC ethical guidelines: “The benefits of research are to be made available to the research population and the local communities from which they were drawn....”

New Zealand

- The informed consent process should describe what will happen after the study, including:

“[W]hether any study intervention will be available to participants after the study and, if so, under what conditions (including any cost to them)...”

<http://neac.health.govt.nz/publications-and-resources/neac-publications/streamlined-ethical-guidelines-health-and-disability>

Nepal

- “The investigator is responsible for... ensuring that appropriate care and relevant follow-up procedures are maintained after the trial for a period that is dependent upon the nature of the disease and the trial and the interventions made.”

Council of Europe, Guide for Ethics Committee Members (2010)

For transnational research: “In anticipation of any beneficial research results related to therapy, the discussion should include how the treatment/preventive agent might be made available locally after the study...”