Taking Stock of the Ethical Foundations of International Health Research: Pragmatic Lessons from the IU–Moi Academic Research Ethics Partnership

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It is a *sine qua non* that research and health care provided in international settings raise profound ethical questions when different cultural and political values are implicated. Yet ironically, as international health research expands and as research on ethical issues in international health research broadens and deepens, we appear to have moved away from discussing the moral foundations of these activities. For international health research to thrive and lead to the kind of benefits it is capable of, it is helpful to occasionally revisit the foundational premises that justify the enterprise as a whole. We draw on the experience of the Indiana University–Moi University Academic Research Ethics Partnership, an innovative bioethics training program co-located in Indianapolis and Eldoret, Kenya to highlight the changing nature of ethical issues in international health research and the ongoing practical challenges.

KEY WORDS: bioethics; international health; research partnership.

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INTRODUCTION

In an authoritative 2007 volume of case studies on international research ethics, a group of prominent National Institutes of Health (NIH) bioethicists noted that while much of the previous decade's debate about international research focused on which standard of care should be provided to participants in clinical trials, "the ethics of international research goes well beyond this important issue."¹ Over the last 5 years, a comprehensive literature in global bioethics has emerged providing ever-more-detailed assessments of informed consent,² the conduct of clinical trials,³ ethics review of research,⁴ post-trial obligations to research participants⁵ and other more specialized topics in genomics,^{6, 7} public health,^{8, 9} sustainability,¹⁰ community engagement,¹¹ and the deployment of biotechnology.¹²

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cultural and political values are involved. Ironically, as international health research expands, especially to countries including India, China, and Brazil,¹³ and as research on ethical issues in international health research broadens and deepens, we appear to have moved away from discussing the moral foundations of these activities—as if the early deliberations about *why* it is ethically justified to carry out research elsewhere, or *which* standards, *whose* guidelines, or *what* principles should be used—have been resolved and now all there is left to do is work out the technical details of consent forms, data management practices and the like.¹⁴ However, for international health research to thrive and lead to the kind of benefits it is capable of, it is helpful to occasionally revisit the foundational premises that justify the enterprise as a whole. Not only will doing so aid in the resolution of practical problems, but the resolution itself may guide further thinking about the foundations. For example, in the early 1990s, ethical arguments for¹⁵ and against¹⁶ the use of a placebo in the ACTG-076 anti-retroviral HIV trial helped focus international discussion on this topic. But the argument stalled for at least a decade, in part because of the cost of providing the "best" standard of care. But once the costs of providing anti-retroviral medicine plummeted,¹⁷ the moral focus of the argument became less tethered to the cost issue. Discussion of the ethical foundations for international health research were informed by specific pragmatic considerations, and vice versa.

THE TUG OF UNIVERSALISM AND THE DEFENSE OF ETHICAL MORAL STANDARDS

The tug of universalism in bioethics can be powerful. The idea that there are moral norms that ought to apply across societies, cultures, time, and geography has an immediate appeal, especially given the long history of human rights abuses and the exploitation of vulnerable persons. For obvious acts like premeditated murder or enslaving people, it is intuitive as a matter of justice to conclude that if it is

wrong in one country to murder or enslave, it should be wrong in another country as well. One attraction of a universalist moral framework is that it sets a common standard for all, discriminating against none. The UNESCO Universal Declaration on Bioethics and Human Rights is an example of this thinking, as it reflects a desire to capture common commitments, even though debate persists about whether it truly rests on an unarguable set of foundational moral norms.^{18, 19}

The universalist tug is especially strong in research ethics where the response to Nazi atrocities—first with the Nuremberg Code and then later the multiple revisions to the World Medical Association's Declaration of Helsinki, and other governance documents²⁰—reflected a commitment to ethical norms that might transcend country, culture or chronology. This type of foundationalism may be too strong to rely upon in all matters of international research ethics,²¹ and one may settle instead for what Beauchamp and Childress defend as a "common morality."²² But this is because not all decisions in health research are as clear as premeditated murder or slavery. Still there is sufficient consensus on many ethical issues, as hundreds of guidelines for human subjects research throughout the world can attest.²³ For example, most guidance documents recommend that obtaining the voluntary informed consent from the research participant and the approval of a duly constituted local institutional ethics review committee are mandatory prerequisites for conducting research with human subjects. But one can satisfy these general requirements and still face challenging new questions: for example, whether alternatives to local review (such as regional or centralized review) should be considered under certain circumstances,^{24, 25} or whether placebo controls can be used when there is an existing (but very expensive) standard of care. On this latter issue, commentators have been split, with some arguing that one universal standard should prevail,²⁶ while others like Resnik argued "we should not expect single standard of research to govern all study designs."²⁷

While the lowered costs of ARVs may have softened the extreme positions on whether the next placebo-controlled trial should occur in a low or middle income country (LMIC), the ethical issues are relevant today for a different reason: because conceptual questions remain about what a *standard* is and how is it different from a principle, a policy or a procedure.²⁸ The potential for confusion is reflected in the recent report of the International Research Panel convened by President Obama's bioethics commission, which summarized the current consensus:

Rules, standards, and practices vary greatly around the globe. Not all transnational or national rules, standards, and practices are the same, nor are they harmonized. In addition, rules may be interpreted or implemented differently as a result of complex

cultural, political, and economic influences. This variation creates a challenge when research occurs across national borders, particularly when rules in one country conflict with, are stricter or more lenient than, or are less developed than rules in another. Despite this variation, almost all international codes and national laws and regulations governing research with human subjects seem to promote the basic principles of respect for persons, beneficence, and justice, and do agree specifically about certain fundamental requirements, such as minimizing risk, obtaining informed consent, and requiring independent review of research.²⁹

Some clarity may have been offered by the prior National Bioethics Advisory Commission, when it distinguished between substantive and procedural ethical requirements.³⁰ Substantive ethical requirements were seen as broadly held (even universal) ethical standards. For example, the ethical principles of respect for persons, beneficence and justice described in the *Belmont Report*³¹ function as substantive ethical requirements; thus, countries may "adopt" the ethical principles developed elsewhere insofar as they recognize their moral value and find them to be useful guides, even if such principles are developed in another country whose political history and traditions are not identical.

In contrast, procedural standards are the operational requirements that effect actual decisions in research. For example, the *Belmont Report's* ethical principles give rise to specific procedural requirements: informed consent, assessment of risk and benefit, and fair selection of research subjects, respectively. Procedural requirements may also extend to the infrastructure and operations of ethics committees, data protection, record keeping and all manner of issues that permit the effective functioning of committees. Most research ethics committees use similar procedural standards (e.g., interdisciplinary review of submitted protocols, regular meetings, and interdisciplinary membership).

Seen in this way, the question "should local or universal ethical standards govern international health research?" would be answered differently depending on whether one was concerned with substantive ethical standards or procedural ones. Two countries can agree to adopt common substantive ethical standards, and also agree to adopt similar procedures. But importantly, countries may also adopt different interpretations of principles, and procedures for implementing them.³² When the Obama bioethics commission noted that "almost all international codes...seem to promote the basic principles of respect for persons, beneficence, and justice," it was claiming that a common set of substantive ethical standards exist. And when it further noted that these same codes "...do agree specifically about certain fundamental requirements, such as minimizing

risk, obtaining informed consent, and requiring independent review of research,” it was affirming that there are a common set of procedural ethical standards that exist.³³ We concur, but as we discuss below, our experience in the Indiana University (IU)–Moi University Academic Research Ethics Partnership reveals more detail about the interaction of both claims.

LESSONS FROM THE IU–MOI ACADEMIC RESEARCH ETHICS PARTNERSHIP

Indiana University has collaborated with Moi University School of Medicine (MUSOM) in Eldoret, Kenya for more than 20 years. In 2001, the program’s major focus shifted towards developing and implementing health care through the Academic Model Providing Access to Healthcare (AMPATH), which in addition to Moi and IU now includes 16 North American universities.³⁴ AMPATH is a comprehensive mission-directed program with a focus on service, education and research. As described in a companion article in this Supplement, AMPATH’s research mission is as impressive in its collaborations as it is in the scope of the projects themselves: clinical trials; health information database studies; community-based trials of innovative care delivery; multiple health services projects, and newer efforts emerging in public health and genetic studies.³⁵ Each of these designs, and others such as comparative effectiveness studies³⁶ raise challenging bioethical questions in international collaborations. So it is noteworthy, that even before this growth in research within AMPATH, its leadership recognized the need for attention to bioethics issues.

THE 2003 MEMORANDUM OF UNDERSTANDING AND 2007 NEEDS ASSESSMENT

With funding from the National Institutes of Health, we convened a workshop in Eldoret in February 2003 with the goal of developing a joint understanding between Moi and IU for conducting research that was sensitive to local values and consistent with accepted principles of research ethics. The meeting highlighted the challenges of seeking consensus on substantive and procedural ethical standards. For example, while all agreed that informed consent was a substantive ethical standard, there were different interpretations on how to obtain informed consent; for example whether it was appropriate for women to permit their husbands to provide consent for their involvement in research. Following 3 days of meetings involving researchers, Institutional Review Board (IRB) members, and senior administrators from both universities, a Memorandum of Understanding (MOU) was adopted, chosen because of its aspirational quality and commitment “to

describe the common principles that will guide those relationships and activities of the relevant review bodies at both institutions.” The MOU included a set of five “general principles” designed to inform the research relationship between Moi and IU:

- There is mutual recognition of the important contributions that the institutions have made and will make, towards advancing knowledge in the health sciences.
- That ongoing communication and consultations are important means for anticipating and addressing issues of mutual interest.
- That respecting and recognizing integrity and authority of each institution is indispensable.
- That different but mutually acceptable policies and procedures may be developed or adopted by each institution to guide the conduct of research, ethical review and other matters relating to this collaboration.
- In the event that disagreements or conflicts arise, the institution will strive to resolve them amicably and respectfully.

The MOU was signed by the highest-ranking institutional officials at both universities and disseminated widely. Two years later, we undertook a needs assessment to determine the extent to which the ideal of the MOU had permeated the research cultures at both universities, to identify any barriers to the collaborative spirit outlined in the MOU, and to recommend specific policy and educational steps to take for overcoming these barriers.³⁷ The needs assessment confirmed a general level of agreement about the importance of appealing to common principles of research ethics, but demonstrated incomplete knowledge about the respective national regulatory requirements for ethics review of collaborative international research, about the actual procedures required by both institutions, and most importantly, about how to resolve any disagreements between the Moi and IU ethics review committees when conflicting interpretations occurred. The following verbatim responses from the needs assessment illustrate some of these points.

A member of the Moi Institutional Research Ethics Committee (IREC) observed:

“I don’t think there are any (policies and procedures) as of now for international protocols, but we just take them through the review procedures that are there...just like any other protocol that would be submitted whether it’s done internally or externally.”

An Indiana University administrator observed that:

“I think that the general elements [of research ethics review] are certainly the same. Subject protection, informed consent and no coercion at all. I think that there has been an obvious sensitivity to cultural

issues. I think there has been some recognition that the informed consent process might be somewhat different in a developing country and that...the written informed consent may not be the appropriate vehicle to obtain [in Kenya].”³⁸

These responses reminded us that an agreement on paper, regardless of how collaborative the spirit that informed it or the language adopted, is only a small component of a true partnership. It confirmed that buried deep within the DNA of international collaborative research is a recognition that cultural, linguistic and social differences between collaborators pose critical challenges to the success of research partnerships between institutions.³⁹ Similarly, differences in the respective political histories of countries, just like the differences in the distribution of prosperity and poverty, will inevitably impact ethical reflection. A true partnership is a fluid process that requires ongoing discussion of cultural similarities and differences, institutional commitment to mutual problem-solving, and a concerted effort by collaborators to understand each other as the partnership matures.

Bioethics Training. The MOU and needs assessment also foreshadowed that ongoing training in ethical issues in human subject research was necessary for the success of the partnership. With funding from the Fogarty International Center, we established in 2009 the Indiana University-Moi University Academic Research Ethics Partnership (IU-Moi AREP), a bioethics training program co-located in Indianapolis and Eldoret, Kenya.⁴⁰ The IU-Moi AREP created new Master’s degrees in international research ethics at each university, an annual 3-day teaching workshop on “Teaching Skills in International Research Ethics (TaSkR)” that rotates between Indiana and Kenya, and a suite of short courses. To date, more than 250 Moi and IU-based faculty and students have participated in one or more of these programs, and more than 20 graduate students are enrolled in the two MA programs. These initiatives have already borne fruit as trainees have taken up positions within research administration offices at both universities, been appointed to national committees, and contributed to the scholarly literature.^{41, 42, 43, 44, 45}

Ethics Review. The IU-Moi AREP also provides a platform to better understand the ethical issues that arise in the review and approval process of research involving human subjects. Such assessments always require careful judgments—about risk in relation to benefit, about whether information is appropriately conveyed in a consent form, or whether remuneration is exploitative or excessive. These issues are often more vexing when two ethics review committees working in different countries are

assessing the same protocol using different regulations or guidelines. This explains why efforts at harmonization generally have proven challenging.^{46, 47} Ethics review is also where the difference between substantive and procedural ethical requirements become readily apparent. Practically speaking, ethics committees are the procedural instruments for translating substantive ethical standards into practical research protections for human participants.

Variation exists between ethics review committees because governance systems have been implemented to varying degrees in many African countries, each with nuanced differences.⁴⁸ Such developments are, in part, a response to the growth in international collaborative health research generally.⁴⁹ But developing capacity for ethics review in LMICs involves more than establishing ethics review committees and regulatory processes; it requires a conceptual framework that builds upon geopolitical, cultural and other factors, including the country’s stage of development and the institution’s organizational culture.⁵⁰ Hyder and colleagues call these factors, “enabling conditions.”⁵¹

Our two universities have experienced first-hand the challenges of applying substantive ethical principles in settings with limited structure and capacity. Both have ethics review committees. Like all U.S. universities that receive federal funds, Indiana University has multiple IRBs. The Institutional Research and Ethics Committee (IREC) at the Moi University Teaching and Referral Hospital (MTRH) was established in 1993. Its role is identical to any US IRB and has received accreditation from the Kenyan National Council of Science and Technology (NCST).⁵² Like Indiana University, Moi University has a Federal-Wide Assurance from the U.S. Office for Human Research Protections (OHRP), which places requirements on the institution to comply with US research regulations such as the Common Rule (including the *Belmont Report*). IREC consists of sixteen members, nine of whom are MUSOM faculty members, as well as six staff members from the Moi Teaching and Referral Hospital.

The current review systems at both universities provide adequate and effective review; however, it can be inefficient. Currently, collaborative research between Moi and IU investigators involves a system of separate-but-linked review in which protocols are submitted simultaneously to both committees. In each committee (one at Moi and one at Indiana), one or two primary reviewers are assigned who independently provide comments to the investigators. This sometimes means that investigators have to interact with the IRBs in two different countries. Each IRB independently makes approval decisions in their regular committee meetings. As an investigator deals with reviewer comments, it is their responsibility to update the other committee of any changes incorporated into their proposal, thereby ensuring the final document approved by the two committees is the same.

There are obvious benefits to this separate-but-integrated process: much is gained from the expertise that both institutions have about human subjects protection and their knowledge of local context, especially for issues involving informed consent. But there are challenges as well, not the least of which is the amount of time it takes for the give and take of response and review; and at times issues considered important by one committee are not given the same level of scrutiny in the other. For example, the IU IRB and Moi's IREC both approved a recent protocol for assessing dosing for pediatric patients receiving antiretroviral therapy,⁵³ although the investigators faced different concerns and questions in the two committees. Other projects have been approved by one committee, and not by the other. In general, therefore, the two committees function in a similar way and use similar procedural standards for decision making. They also, use the same substantive ethical standards. But where differences sometimes arise is in the application and interpretation of these standards reflecting their understanding of the way the system works, and the relevance of local context, culture and norms. In many instances, the review considerations are identical, but we have noted that the Indiana IRB often defers to IREC on local contextual issues in the proposal, sometimes reflecting the respect for difference and recognition of local expertise. But in other instances, committees may reach different decisions.

This can be frustrating for investigators. As stated in the 2003 MOU, when "disagreements or conflicts arise, the institutions strive to resolve them amicably and respectfully." In an attempt to improve the system of dual local review, we proposed the establishment of a joint Institutional Review Board, a committee that would be independent from both universities, with equal committee representation from both institutions, joint chairpersons, and a harmonized review structure. We recognized significant issues with such an approach. First, it challenged the prevailing paradigm of "local review," recognized both in regulation and accepted guidance documents. Second, it would require the support of both universities as reflected in their willingness to permit the new committee to undertake reviews on their joint behalf. We also realized that it would require a significant psychological shift in thinking about "our" ethical commitments and "their" ethical commitments. It was a new opportunity for both universities and both countries. Neither had undertaken a task of this kind in which a committee was not beholden to one institution (or one country). The proposal for a joint IRB was to be the first anywhere in the world. Critically important to this effort was the requirement that the new committee be acceptable to the relevant national regulatory bodies responsible for oversight in each country. In other words, it was an ideal opportunity to "take stock" of the ethical foundations of international research ethics.

With NIH funding, we undertook a year-long study that sought to establish the ethical and legal framework for such a committee, and develop appropriate structures, procedures, training programs and sustainability plans. From 2010 to 2011, considerable progress was made. Research was undertaken to better understand the nature of the US and Kenyan regulatory systems and whether any obvious impediments existed. None were found. Indeed, while nothing in the Common Rule or FDA regulations explicitly permits establishment of a joint IRB, nothing prohibits it either. Similarly in Kenya, the National Council on Science and Technology (NCST) has the authority to delegate the establishment of new ethics committee expressly through Chapter 250 of the Laws of Kenya,⁵⁴ though approval must also be provided by the Kenyan National Bioethics Committee. Any new committee established in Kenya that reviews research undertaken in Kenya is expected to satisfy NCST requirements described in the *Guidelines for Ethical Conduct of Biomedical Research Involving Human Subjects in Kenya*.⁵⁵

Consultations with institutional officials at both universities occurred, as did meetings with senior regulatory officials from OHRP, the FDA and the NCST, which confirmed our interpretation of US and Kenyan regulations. At the same time the consultations were occurring, some structures were being developed at IU and Moi: provisional chairpersons from each institution were identified, draft standard operating procedures were developed, lists of provisional committee members were constructed, and a mock IRB meeting was held in Indianapolis in April 2011, at which a protocol was reviewed by more than 20 provisional representatives from IU and Moi. We were on track to establish the joint committee.

Despite this significant, collaborative progress, the IU Moi Joint Ethics Review Committee was not established. Why not? The Chair of the Kenyan National Bioethics Committee informed us that a joint committee would not be approved because "the question of a joint International Ethic[s] Review Committee does not arise since Moi University has the capacity to review the proposals."⁵⁶ In follow-up discussions, we also understood that by establishing such a committee and allowing it to review protocols undertaken in Kenya, it was perceived to infringe on Kenya's national autonomy. The decision from the Kenyan NBC was decisive, authoritative and copied to senior leadership at Moi. Understandably, the Moi-IU team was disappointed and confused, as no formal request had been made to the National Bioethics Committee to approve the joint committee (given that the project was still underway in December 2011) and the results had not been formally reported. Subsequently, there has been ongoing communication to explore other options for encouraging the efficient and effective review of research, which include establishing subcommittees, harmonizing meeting schedules, and giving

due consideration to seeking the “equivalent protection” status provided by the US Common Rule (45 CFR 46.1010 (h)). It is unclear what the fate of a new committee might be, but the experience was instructive.

LESSONS LEARNED

It is healthy to periodically assess whether we hold fast to the same values and commitments we previously held in light of new experiences and information. It is one thing to establish and rely on a defensible moral framework to guide thinking, it is quite another to blindly and uncritically adhere to its tenets. Nine years after the Eldoret workshop that crafted a first-in-the-world MOU on ethical responsibilities between collaborating universities, and 7 years after a needs assessment to better understand the impediments to implementing the values found in the MOU, health researchers at these two universities continue to take stock of the ethical foundations of their collaborative research experiences. This may be the most important lesson jointly learned: that working through ethical issues is an ongoing process, not an end goal.

We also learned that building bioethics capacity is achieved when support is available, clear goals are set, and leadership is provided. Faculty and students are being trained in international research ethics. The IU Moi AREP is being utilized by AMPATH to provide bioethics expertise. Building joint bioethics capacity is a collaborative effort, and we have learned from each other. Moi collaborators want to learn U.S. procedures, but they also strive to understand the ethical basis for them, rooted in a socio-political history very different from their own. Similarly, Indiana University collaborators want to learn about Kenyan procedures and become more sensitive to the diverse cultural values, as well as economic, historical and political factors that inform their research enterprise. Finally, in our experience trying to establish a joint IRB, we learned that in spite of agreement at the local level to develop new procedures to enhance research, there may remain strongly held views about the impact of such innovation on other deeply held ethical values. Taking stock is indeed an ongoing process.

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REFERENCES

1. Lavery JV, Grady C, Wahl ER, Emanuel EJ, eds. Ethical Issues in International Biomedical Research. New York: Oxford University Press; 2007.
2. Molyneux CS, Wassenaar DR, Peshu N, et al. 'Even if they ask you to stand by a tree all day, you will have to do it (laughter)...!': community voices on the notion and practice of informed consent for biomedical research in developing countries. *SocSci Med*. 2005;61(2):443–54.
3. Shapiro HT, Meslin EM. Ethical issues in the design and conduct of clinical trials in developing countries. *N Eng J Med*. 2001;345:139–41.
4. Emanuel EJ, Wendler DJ, Killen J, Grady C. What makes clinical research in developing countries ethical? the benchmarks of ethical research. *J Infect Dis*. 2004;189:930–7.
5. Lavery JV, Bandewar SV, Kimani J, et al. 'Relief of oppression': an organizing principle for researchers' obligations to participants in observational studies in the developing world. *BMC Publ Health*. 2010;10:384.
6. Smith AC, Mugabe J, Singer PA, et al. Harnessing genomics to improve health in Africa—an executive course to support genomics policy. *Health Res Policy Syst*. 2005;3(1):2.
7. Parker M, Bull SJ, de Vries J, Agbenyega T, Doumbo OK, Kwiatkowski DP. Ethical data release in genome-wide association studies in developing countries. *PLoS Med*. 2009;6(11):e1000143.
8. Gitau-Mburu D. Should public health be exempt from ethical regulations? Intricacies of research versus activity. *East Afr J Public Health*. 2008;5(3):160–2.
9. Emanuel EJ, Wendler D, Killen J, Grady C. What makes clinical research in developing countries ethical? the benchmarks of ethical research. *J Infect Dis*. 2004;189:930–7.
10. Byskov J, Bloch P, Blystad A, et al. Accountable priority setting for trust in health systems—the need for research into a new approach for strengthening sustainable health action in developing countries. *Health Res Policy Syst*. 2009;7:23.
11. Marsh VM, Kamuya DK, Parker MJ, et al. Working with concepts: the role of community in international collaborative biomedical research. *Public Health Ethics*. 2011;4(1):26–39.
12. Mfutso-Bengo JM, Muula AS. Potential benefits and harm of biotechnology in developing countries: the ethics and social dimensions. *Afr J Med Med Sci*. 2007;36(Suppl):63–7.
13. Thiers FA, Sinskey AJ, Berndt ER. Trends in the globalization of clinical trials. *Nat Rev Drug Discov*. 2008;7:13–4.
14. Meslin EM. Achieving Global Justice in Health Through Global Research Ethics: Supplementing Macklin's "Top-Down" Approach with one from the "Ground Up". In Green RM, Aine D, Jauss SA, eds. *Global Bioethics: issues of Conscience for the Twenty-first Century*. Oxford University Press; 2009:163–177.
15. Varmus H, Satcher D. Ethical complexities of conducting research in developing countries. *N Eng J Med*. 1997;337:1003–5.
16. Lurie P, Wolfe SM. Unethical trials of intervention to reduce perinatal transmission of the human immunodeficiency virus. *N Eng J Med*. 1997;337:853–5.
17. Waning B, Kaplan W, King AC, et al. Global strategies to reduce the price of antiretroviral medicines: evidence from transactional databases. *Bulletin of the World Health Organization* 2009;87:520–528. doi: 10.2471/BLT.08.058925. Available at: <http://www.who.int/bulletin/volumes/87/7/08-058925/en/> Accessed Dec. 2012.
18. MacPherson CC. Global bioethics: did the universal declaration on bioethics and human rights miss the boat? *J Med Ethics*. 2007;33:588–90. doi:10.1136/jme.2005.013797.
19. Adorno R. Global bioethics at UNESCO: in defence of the universal declaration on bioethics and human rights. *J Med Ethics*. 2007;33:150–4. doi:10.1136/jme.2006.016543.

20. Codes, Declarations and Other Ethical Guidance for Research with Humans in: **Emanuel EJ, Crouch RA, Grady CC, Lie RK, Miller FG, Wendler DD, eds.** The Oxford Textbook of Clinical Research Ethics. New York: Oxford University Press; 2008:123–197.
21. **ten Have H.** Foundationalism and Principles. In: **Chadwick R, ten Have H, Meslin EM, eds.** The Sage Handbook of Health Care Ethics. London: Sage Handbooks; 2011:20.
22. **Beauchamp TL, Childress JF.** Principles of Biomedical Ethics. 6th ed. Oxford University Press; 2009.
23. The US Office for Human Research Protections maintains a database of international guidelines, which is updated periodically. It includes more than 1000 documents from over 100 countries. Available at <http://www.hhs.gov/ohrp/international/intlcompilation/intlcompilation.html>. Accessed October 26, 2012
24. **Hyder AA, Dawson L, Bachani AM, Lavery JV.** Moving from research ethics review to research ethics systems in low-income and middle-income countries. *Lancet*. 2009;373(9666):862–5.
25. **Wood A, Grady C, Emanuel EJ.** Regional ethics organizations for protection of human research participants. *Nat Med*. 2004;10(12):1283–8.
26. **Greco DB.** Revising the declaration of Helsinki: ethics vs. economics or the fallacy of urgency. *Canadian HIV/AIDS Policy and Law Review*. 2000;5:94–7.
27. **Resnik DB.** The ethics of HIV research in developing nations. *Bioethics*. 1998;12:286–306.
28. **Macklin R.** Appropriate Ethical Standards. In: **Emanuel EJ, Crouch RA, Grady CC, Lie RK, Miller FG, Wendler DD, eds.** The Oxford Textbook of Clinical Research Ethics. New York: Oxford University Press; 2008:711.
29. Presidential Commission for the Study of Bioethical Issues. Research Across Borders: Proceedings of the International Panel of the Presidential Commission for the Study of Bioethical Issues. Washington DC; 2011:6.
30. National Bioethics Advisory Commission. Ethical and Policy Issues in International Research: Clinical Trials in Developing Countries. Washington, DC 2001. <http://bioethics.georgetown.edu/nbac/clinical/Vol1.pdf> Accessed December 2012.
31. National Commission for the Protection of Human Subjects of Biomedical and Behavioral Research. *The Belmont Report*. Ethical Principles and Guidelines for the Protection of Human Subjects of Research (April 1979). <http://www.hhs.gov/ohrp/humansubjects/guidance/belmont.html> Accessed December 2012.
32. **Orentlicher D.** Universality and its limits: when research ethics can reflect local circumstances. *J Law Med Ethics*. 2002;30(3):403–10.
33. World Health Organization. Operational Guidelines for Ethics Committees that Review Biomedical Research. 2000;DR/PRD/ETHIC/2001.
34. **Einterz RM, Kimaiyo S, Mengech HN, et al.** Responding to the HIV pandemic: the power of an academic medical partnership. *Acad Med*. 2007;82(8):812–8.
35. **Tierney WT, Nyandiko WN, Siika AM et al.** MMED, MSc “These are Good Problems to Have...”: Establishing a Collaborative Research Partnership in East Africa
36. **Chalkidou K, Tunis S, Lopert R, Rochaix L, Sawicki PT, Nasser M, Xerri B.** Comparative effectiveness research and evidence-based health policy: experience from four countries. *Milbank Q*. 2009;87(2):339–67.
37. **Sidle JE, Were E, Wools-Kaloustian K, et al.** A needs assessment to build international research ethics capacity. *J Empir Res Hum Res Ethics*. 2006;1(2):23–38.
38. Some of the quoted material is from the original article. Other material from **Meslin EM, Sidle JE, Wools-Kaloustian K, Were E, Salmon K, Chuani C.** International Research Ethics: A Needs Assessment of Research Ethics Capacity Final Report and Responses. Available at: <http://hdl.handle.net/1805/639>. Accessed December 2012
39. **Serrano LD, Linares AM.** Ethical principles of biomedical research on human subjects: their application and limitations in latin America and the Caribbean. *Bulletin of the Pan Am Health Organ*. 1990;24(4):469–79.
40. **www.bioethics.iu.edu/AREP** This program is one of more than 20+ funded by the Fogarty International Center's International Research Ethics Education and Curriculum Development Award, the purpose of which is to “develop masters level curricula and provide educational opportunities for developing country academics, researchers and health professionals in ethics related to performing research involving human subjects in international resource poor settings” (<http://www.fic.nih.gov/programs/pages/bioethics.aspx>) Accessed December 2012.
41. **Shaffer DN, Greene JY, Kimaiyo S, et al.** Sidle. Equitable treatment for HIV/AIDS clinical trial participants: a focus group study of patients, researchers, and health administrators in western Kenya. *J Med Ethics*. 2006;32:55–60.
42. **Vreeman RC, Nyandiko WM, Meslin EM.** Pediatric Assent for a Study of Antiretroviral Therapy Dosing for Children in Western Kenya: A Case Study in International Research Collaboration. *Journal of Empirical Research in Human Research Ethics*. 2009;3–16. DOI:10.1525/jer.2009.4.1
43. **Were MC, Meslin EM.** Ethics of implementing electronic health records in developing countries: points to Consider. *AMIA Annu Symp Proc*. 2011;2011:1499–505. Epub 2011 Oct 22.
44. **Pappas RK, Gakinya BN, Martino S, et al.** Ethical issues in a Stage 1 cognitive-behavioral therapy feasibility study and trial to reduce alcohol use among HIV-infected outpatients in western Kenya. *J Empir Res Hum Res Ethics*. 2012;7(3):29–37.
45. **Vreeman R, Kamaara E, Kamanda A, Ayuku D, Nyandiko W, Atwoli L, Ayaya S, Gisore P, Scanlon M, Paula Braitstein P.** A qualitative study using traditional community assemblies to investigate community perspectives on informed consent and research participation in western Kenya. *BMC Med Ethics*. 2012;13:23.
46. **Califf RM, Morse MA, Wittes J, et al.** Toward protecting the safety of participants in clinical trials. *Control Clin Trials*. 2003;24(3):256–71.
47. **Lavery JV.** A culture of ethical conduct in research: the proper goal of capacity-building in international research ethics. Working paper WG2:5 Geneva:WHO, Commission on Macroeconomics and Health. 2001.
48. **Hyder AA, Harrison RA, Kass N, Maman S.** A case study of research ethics capacity development in Africa. *Acad Med*. 2007;82:675–83.
49. **Thiers FA, Sinskey AJ, Berndt ER.** Trends in the globalization of clinical trials. *Nat Rev Drug Discov*. 2008;7:13–4.
50. **Lavery JV.** A culture of ethical conduct in research: the proper goal of capacity-building in international research ethics. Working paper WG2:5 Geneva: WHO, Commission on Macroeconomics and Health. 2001.
51. **Hyder AA, Dawson L, Bachani AM, Lavery JV.** Moving from research ethics review to research ethics systems in low-income and middle-income countries. *Lancet*. 2009;373(9666):862–5.
52. National Council for Science and Technology (Kenya). Guidelines for ethical conduct of biomedical research involving human subjects in Kenya. NCST No. 45; 2004.
53. **Vreeman RC, Nyandiko WM, Meslin EM.** Pediatric assent for a study of antiretroviral therapy dosing for children in Western Kenya: a case study in international research collaboration. *J Empir Res Hum Res Ethics*. 2009;4(1):3–16.
54. National Council for Science and Technology (Kenya). Research clearance in Kenya: procedures and guidelines. Nairobi, Kenya: No.15; 1984.
55. National Council for Science and Technology (Kenya). Guidelines for Ethical Conduct of Biomedical Research Involving Human Subjects in Kenya. Nairobi, Kenya: No. 45;2004.
56. Letter from Kirana Bhatt to Eric Meslin and David Ayuku, December 8, 2011