Multinational Research and Capacity Building
Department of Bioethics, NIH

Multinational Research

Background: Multinational research is essential to understanding and ultimately controlling diseases of global importance, but is beset with complex ethical issues. An overarching ethical concern is the possible exploitation of vulnerable individuals or populations. Much multinational research is sponsored by developed-world entities (both public and private) and conducted in developing countries. Exploitation, usually understood as one party taking unfair advantage of the vulnerability of another, is more challenging in the context of multinational research conducted in developing countries because of background disparities in health, health resources, and power between developed and developing countries.

The Department's initiatives aim to better understand the ethical complexities of multinational research, covering various specific topics in the ethics of multinational research and situating this research within a larger examination of issues of exploitation and globalization. Addressing the ethical issues in multi-national research will also help to promote and facilitate research in diseases that are responsible for a major portion of the global burden of disease.

Beginning in the fall of 2001, the Department focused a substantial portion of its research on conceptual and empirical issues related to the ethics of multinational clinical research. Many of these projects were collaborations with researchers from developing countries, including many NIAID supported researchers. Since that time over 70 research papers have been published. Between 2007 and 2010, over 30 research papers have been published by members of the Department in peer reviewed journals including *Science*, *The Lancet*, *JAMA*, *PLoS Medicine*, *American Journal of Public Health,* and the leading bioethics journals. Some of these articles represent the only scholarly work on a topic; others are already well-cited “classics” in the literature. Between 2007 and 2010 we have published on the following topics:

- Empirical studies of informed consent and disclosure of genetic risk in different countries
- Empirical studies of attitudes to the transfer of samples across borders among researchers and policy makers
- Empirical studies of attitudes to benefits, burdens and inducements in research
- Conceptual analysis of exploitation in multinational research
- Conceptual analyses of Fair Benefits, Reasonable Availability, and Responsiveness
- Conceptual analyses of the obligation to provide ancillary care and post-trial benefits to study participants

In the following we discuss empirical and conceptual research separately.

Empirical research

Section:	Ethics of Human Subjects Research	
Principal Investigators:	Christine Grady, R.N., Ph.D. Reidar Lie, M.D., Ph.D. David Wendler, Ph.D.	
Collaborators:	**Bioethics:**	Ezekiel Emanuel, M.D., Ph.D. Joseph Millum, Ph.D. Ben Krohmal Jesse Chao Lindsay Sabik Carrie Thiessen Bryan Townsend Elizabeth Wahl Stacy Elmer
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Background: Critical to an appropriate analysis of the ethical issues associated with multinational research are the perspectives of the research participants. Potential research participants in developing countries are sometimes thought to be unable to provide informed consent. Poverty, limited education, limited access to health care and limited familiarity with research might make it difficult to understand the nature of the research being proposed or compel them to enroll regardless of the details. Nonetheless, there is limited empirical data describing the quality of informed consent in developing countries that would allow these concerns to be assessed.

Another concern is exploitation. Research that benefits people in the developed world while exposing people in developing countries to risks and burdens is considered a quintessential example of exploitation. There is a spectrum of multinational clinical research, from research that can bring significant benefit to developing country participants and economies to research that actually can make individuals or communities worse off. Understanding the spectrum of research, possible kinds of benefits and harms, and the perceptions of those involved in research as to what is fair and what is exploitative could help to minimize exploitative research. Yet, there are limited empirical data describing the views of developing country participants' or researchers on these issues.

Finally, clinical researchers and IRBs around the world interpret national and international guidelines, decide whether certain trials adhere to ethical standards, and what information to provide during the process of informed consent. Again, there has not been any comprehensive assessment of the views of clinical researchers or IRBs throughout the world about controversies in multi-national research, or of how various ethical concepts, like informed consent or post-trial access, are put into practice

Departmental Research Initiatives: The Department of Bioethics continue to undertake several empirical research initiatives to complement our conceptual and policy work related to the ethics of multinational research. The primary aim of this empirical work is to understand how ethical guidelines work in practice and explain how those involved in research think about clinical research, the quality of their consent, their expectations, and their views about research risks and benefits, stored tissue research, and international guidelines and controversies.

ESPRIT Risks and Benefits

Commentators argue that some multinational clinical research exploits patient participants for the benefit of others. To evaluate this concern, individuals from Argentina, Brazil, and Thailand who had been participating in the ESPRIT study for at least 6 months were invited to complete a self-administered survey on their experience and attitudes. ESPRIT is an NIH sponsored multinational Phase III randomized trial of interleukin-2 in HIV disease. This survey built on previous research studies conducted by the Department with ESPRIT participants and PIs when they started ESPRIT (Pace et al 2005; Pace et al 2006; Sabik et al 2005).

We surveyed 582 individuals from Argentina, Brazil, and Thailand who were participating in the ESPRIT study. Respondents who had been participating for an average of 2 years were asked about the benefits and burdens of participating in ESPRIT using a self-administered survey. Most respondents, 91%, in the IL-2 treatment arm and 79% in the no IL-2 control arm reported medical benefits from their participation. In addition, 68% in the IL-2 treatment arm and 60% of the no IL-2 controls reported non-medical benefits. Given that respondents, including those in the control arm, reported medical and non-medical benefits and burdens from their research participation, investigators and review committees should be aware of and respond to the potential for research participants to experience benefits and burdens that are unrelated to the intervention being tested (Lazovski et al 2009).

These same ESPRIT participants were also asked to describe the reasons they continued to participate in ESPRIT over time. Most respondents said they continued to participate in the ESPRIT study in hopes of benefiting personally. The majority also recognized that by participating in ESPRIT they were contributing to helping others; they experienced pride regarding this contribution and considered it an important reason to continue to participate. These results indicate that it is possible for patient participants, even those seeking treatment for a life-threatening illness, to recognize and embrace the goals of the research in which they participate (Wendler et al 2008).

Rakai Risks, Benefits and Voluntariness

In collaboration with the Rakai Health Services Program (RHSP) in Rakai District Uganda, the department developed a study to determine what residents there — both research participants and non-participants — perceive to be the benefits and risks of having research activities in their community. Complementary surveys were developed for research participants in three different RHSP studies, for individuals identified as community leaders, those who declined participation in continuing RHSP studies, and individuals in neighboring communities unaffiliated with RHSP. A total of 915 individuals participated in the survey. The vast majority viewed research as beneficial both to them as individuals and to their communities, although some, mostly minor, risks were identified (Thiessen et al. 2007). In response to questions regarding individual compensation and post-trial community benefit from a hypothetical HIV vaccine study, the majority thought that researchers should provide benefits. However, relatively few identified their preferred individual benefit as money or the preferred community benefit as the vaccine if proven effective. Instead, respondents suggested provision of health care services of various kinds, treatment for people with HIV infection, and other benefits. (Grady et al 2008).

Rakai Project data from a randomized, community based trial of intensive STD control, the STD Control for AIDS Prevention Trial, were analyzed to assess the question of whether people feel compelled to participate in research. The analysis examined how many times people refuse to participate when offered the chance to enroll (7.1 percent of eligible participants did not consent), how frequently they withdraw after enrollment (11.0 percent of participating respondents subsequently withdrew), and how frequently they refuse to participate in certain aspects of the research. A significant percentage of both men and women refused to provide blood samples, urine samples, and a high percentage of eligible women refused to provide vaginal swabs. Such refusal suggests that pressure either from the research team, poverty, or lack of access to health care services does not always compel people to agree to participate or stay in a study (Nalugoda et al 2009).

Multi Country Stored Sample Survey

There is controversy regarding the ethics of research on stored biological samples. Much debate has ensued in the United States over this issue. Less is known about the attitudes of those involved in research internationally. The Department previously surveyed the opinions of research participants. In this period, the Department conducted a large international survey of researchers and policy makers who work with or are otherwise involved with stored samples to understand their attitudes regarding appropriate consent for using samples in research and issues that arise in collaborative research when human samples are collected in one country and analyzed in another. 1,436 researchers, policy makers and members of IRBs in India, Korea, Egypt, Japan, and China were surveyed. While a large number of the respondents would allow sample donors to give consent to future research, a large proportion would not allow blanket, unspecified consent to future research, ranging from 45% in India to 59% in Korea. We also asked the respondents to explain the reasons for their decisions, what types of options should be given to subjects, and what conditions should be placed on future research (Matsui et al. 2009). This skepticism of researchers and policy makers about blanket consent is in marked contrast with what previous research has shown about donor preferences for future research; donors generally view blanket consent for future research as relatively unproblematic.

The same group was also surveyed on their attitudes to ethical issues associated with international transfer of samples. These issues received increased attention with the decision by the Indonesian Minister of Health to refuse to share its H5N1 influenza samples with the international community for influenza surveillance purposes, unless such sharing of samples is tied to specific, binding benefit arrangements, and guaranteed access to a vaccine that is produced using the samples. The results of our survey showed considerable sympathy with this position among our respondents (Zhang et al 2010).

Informed consent and risk disclosure

One study evaluated participant understanding and participation rates of two different approaches to obtaining informed consent, using 2,192 research subjects in a genetic cohort study in Japan (Matsui et al. 2007). One group received the routine approach consisting of written materials and an oral explanation. The other group received a more intense approach consisting of educational lectures and group meetings. The study showed complex relationships between self perceived understanding and reading of the background material among the two groups, raising questions about the value of the informed consent forms.

1857 subjects in an ongoing Japanese population-based genetic cohort were asked at entry about their preferences with regard to being recontacted by researchers in the future and whether they wanted to receive reports on their individual genetic results if genetic problems relevant to their health are discovered for which efficacious interventions might be available (Matsui et al 2008). Most of the donors wished to be recontacted and receive reports, but some did not want any reports. Those who were younger, former/current drinkers, or had at least one parent who had had cancer were more likely to want the results, while those who had at least one sibling with a medical history of cancer were less likely to want the results.

Initial responses to questionnaires used to assess participants' understanding of informed consent for clinical trials of malaria vaccines using similar investigational products and protocols carried out in the US and in Mali were tallied. Since similar tools were used to assess the understanding of prospective participants at all study sites, the data allows for a comparison between the US and Malian informed consent processes. 92% of answers by United States participants and 85% of answers by Malian participants were correct. These results do not support concerns about systematic low understanding among research participants in developing versus developed countries. To our knowledge, this is the first study that directly compares the quality of understanding of participants in clinical trials at sites in developed and developing countries (Miller et al 2010).

Impact of Research: The Department's research represents a substantial contribution to the empirical literature on the key ethical issues associated with conduct of research both from the perspective of participants and researchers. The findings challenge the assumption made by many that poor resources are inherently exploitative and lead to defects in the informed consent process. The surveys on attitudes to ethical issues related to stored tissue samples represent the only systematic data from developing countries.

Future Research Initiatives (PIs in parentheses):

A large multinational collaboration is underway evaluating the comprehension and satisfaction of research participants (up to 4000) after being randomized to a standard consent form or a simpler, concise consent form. Participants are newly diagnosed with HIV infection and randomly assigned to either start antiretroviral medicines immediately upon study entry or wait until their CD4 + T cells drop to 350/mm^3. In addition to evaluating the consent of research participants, we plan to conduct an analysis of changes made to consent forms by IRBs (Christine Grady).

Development of a resource to assist researchers with cultural barriers to obtaining informed consent. This will involve the collection, analysis, and dissemination of examples of culturally sensitive novel methods that other researchers have developed to improve understanding and ensure voluntariness when conducting research in non-Western societies (Christine Grady and Joseph Millum).

A project to quantify the extent and type of phase 1 or early phase research conducted in low to middle-income countries (Christine Grady)

A project to determine the phases, disease targets, types, and amount of multinational research being conducted in developing countries (Seema Shah).

An empirical study of a comparison of a short and a long informed consent form in Japan has been submitted for publication, and a third paper will be published on the survey of investigator attitudes to transfer of samples across borders. A study of participant attitudes to informed

consent to future research and feedback of results in a genetic cohort study is being planned (Reidar Lie).

Conceptual Research

Section:	Human Subjects Research	
Principal Investigators:	Ezekiel Emanuel, M.D., Ph.D. Christine Grady, R.N., Ph.D. Reidar Lie, M.D., Ph.D Joseph Millum, PhD Seema Shah, JD Henry Richardson, Ph.D., J.D., M.P.P (Visiting Scholar) David Wendler, PhD Alan Wertheimer, Ph.D.	
Collaborators:	**Non-NIH Researchers:**	Jennifer Hawkins, Ph.D. Gopal Srenivasan John Barton Thomas Pogge

Background: Over the last two decades, the ethics of research in resource poor settings has received widespread attention in the bioethics literature. Many commentators and international guidelines have argued that 1) trial participants in resource poor settings are more vulnerable to exploitation compared with trial participants in richer countries; 2) trial designs that are unethical in resource rich settings are also unethical in resource poor settings; 3) researchers have obligations to ensure access to care for the health problems of research participants that are not being dealt with by the host country health care system; 4) trials in resource poor settings have to study products aimed at host country markets; and 5) prior agreements ensuring reasonable availability of such products have to be in place before research is approved. Only if certain additional conditions for research in resource poor settings are fulfilled, will one avoid exploitation of vulnerable subjects in such settings. Critics, however, have pointed out that these well-intentioned requirements aiming at ensuring access to beneficial care may have the paradoxical effect of preventing useful research that can lead to health care interventions that will eliminate access barriers in resource poor settings.

Departmental Research Initiatives: The Department has continued a multi-pronged research program examining current controversies associated with multinational research. This program complements the empirical component, and ranges from philosophical examination of the concept of exploitation to specific recommendations regarding the conduct of clinical research in resource poor settings.

Exploitation in Multinational Research

Philosophical analysis of exploitation

The language of exploitation came to the fore in the context of criticisms of research on vulnerable populations and, in particular, research in underdeveloped societies. Concern about exploitation may have reached its apogee in response to the use of placebo controlled trials of the efficacy of a short course treatment of anti-retrovirals in reducing maternal-fetal transmission of HIV when it was already known that a long-course treatment was effective. Those studies

provoked an outbreak of ethical outrage, even though no research participants were worse off than they would have been if the studies had not been conducted.

Despite the intensity of the outrage, the argument that such research should be prohibited on grounds of exploitation needs careful examination. Moreover, the discussion of exploitation in actual clinical research raises other serious questions:

- If research should be permitted, what do researchers owe research participants if they are to avoid exploitation?
- Must researchers provide ancillary care to participants if they are found to have other diseases?
- Do researchers have post-trial obligations towards participants, including ensuring access to the trial intervention after the study is over?
- What do researchers owe to the host country? Do they have obligations to provide the interventions being studied if the studies prove successful?

Drawing on a seminar organized jointly with Georgetown University, Johns Hopkins University and the Center for Public Policy at the University of Maryland, Ezekiel Emanuel and Jennifer Hawkins edited a book on Exploitation in International Research (2008). The book is organized around two highly controversial actual cases: the testing of the hepatitis A vaccine in Thailand and the proposed testing of an artificial surfactant called Surfaxin in several South American countries. In the book, Wertheimer, Pogge and Arneson, along with participants in the seminar series from Georgetown, Johns Hopkins and the NIH — Jennifer Hawkins, Ezekiel Emanuel, Margaret Little, Alisa Carse, and Andrew Siegel —contributed chapters that discuss exploitation and ways to prevent it in the context of these two cases.

Alan Wertheimer (who previously published the major scholarly analysis of exploitation: Exploitation (Princeton University Press, 1996)) was invited to come to the Department initially as a visiting scholar in the 2005-06 academic year, and then continued as a staff scientist to explore exploitation and its relationship to the ethics of clinical research. In his book, Wertheimer argued that it was of capital importance to distinguish between exploitation that is harmful and non-consensual, and exploitation that is mutually advantageous and consensual. Even if a transaction is exploitative, it does not follow that it should not be allowed. Although it is clear that we should not allow harmful and non-consensual exploitation, it is arguable that we should allow exploitative transactions if the exploited party benefits from the transaction and consents to it. The question as to whether and when clinical research in developing societies is exploitative and whether it should be prohibited if it is exploitative is an issue with profound and far-reaching implications. It is an issue on which more heat has been cast than light, and the Department is seeking to reverse that trend. During this time, Wertheimer has written the entry on Exploitation for the *Oxford Textbook on the Ethics of Clinical Research* which was published by Oxford University Press in 2007.

Chapter 5 of Alan Wertheimer (2010) considers exploitation in international research with a particular focus on the use of placebo controlled trials when proven effective treatment is available. This chapter is a major expansion of his earlier work on exploitation. In Chapter 6, Wertheimer argues that what he calls "the interaction principle" underlies much thinking in research ethics. That principle maintains that the interaction between researcher and subject fundamentally alters what researchers owe to subjects. The interaction principle has two main corollaries. It rejects what he calls the "no worseness claim," which maintains that it cannot be worse for researchers to interact with subjects than not interact with them at all if the subject

benefits from the interaction and consents to it. The interaction principle also entails what he calls "the greater obligation claim." This principle maintains that researchers have greater obligations towards research subjects than to non-subjects even if subjects benefit from the interaction, consent to the interaction, and are better off than non-subjects. The interaction principle underlies many principles that are often invoked in international research, such as responsiveness, reasonable availability, fair benefits, and ancillary care. Wertheimer argues that the principle is more difficult to defend than is often supposed.

Building on this philosophical analysis of exploitation, the Department has published a number of papers falling into two broad categories: 1) what is owed to participants during and after trials and 2) what is owed to the communities in which the trials take place.

Obligations to trial participants: Ancillary Care and Post-trial Benefits

During the course of screening or trial participation, researchers may diagnose their subjects with conditions requiring treatment. Subjects are often tested for certain conditions because it is necessary to exclude them, or because there will be an analysis of the stratified results. In HIV vaccine trials, for example, HIV positive individuals are excluded. On the other hand, in a malaria trial, subjects may be identified as HIV positive so researchers can study the effect of HIV on the degree of protection. The moral issue is what obligations, if any, this places on researchers to ensure care for the conditions identified. One could argue that there are no moral obligations to provide ancillary care not necessary for the design of the study: researchers have an obligation to conduct research, not to provide clinical care. On the other hand, the researchers are often physicians, and have the knowledge and skills necessary to provide treatments that are often not available to their study participants. Does this not place some obligation on them to provide such treatment?

Despite being an on-going ethical concern of medical researchers in the field, the issue of researchers' ancillary care obligations had not been examined systematically in the literature until 2004, when Leah Belsky and Henry Richardson of the Department proposed a framework for when researchers are obligated to provide ancillary care to trial participants. It is based on the notion of entrustment and describes an obligation to provide care if certain conditions are fulfilled. Henry Richardson has since expanded on their initial work, examining the issue of how one can specify the strength of the obligations, based on such factors such as the degree of investigator involvement, whether the disease falls within the scope of what is being studied, and the cost of providing ancillary care (Richardson 2007). Other groups, notably associated with UNAIDS, have argued that one has an absolute obligation to provide ancillary care for needs associated with the disease under study.

The Richardson and Belsky model remains controversial, and has been criticized by other researchers in the department (Dickert et al. 2007). This article criticizes the scope requirement of Richardson and Belsky, arguing that sometimes it may be more important to provide care for conditions that fall outside their scope requirement. The Department in collaboration with Georgetown University convened a group of experts in 2006 to attempt to achieve consensus on investigators' ancillary care obligations (Participants 2008). The members of this workshop emphasized that it is necessary to take into account the health needs of the participants when identifying ancillary care obligations, and not just focus on the scope of investigator interactions. The group explicitly argued that the ancillary-care obligations of researchers and their sponsors

are not limited to addressing the disease or condition that is the target of the research, nor do they necessarily need to provide treatment for everything related to that disease or condition.

The subject of ancillary care has also been the topic of one of the Ethics Grand Rounds organized by the Department and a subsequent publication (Dickert and Wendler 2009). An investigator planning a study in Africa of the prevalence of pulmonary hypertension in children with severe malaria anticipated that she and her team would encounter significant unmet health needs during the course of the study. She recognized that study procedures, particularly echocardiography, might identify and diagnose conditions that were not treatable within the local health system due to resource constraints. This article applies the framework developed by Belsky and Richardson, analyzes the question of investigators' responsibilities to meet participants' needs for ancillary care, and argues that investigators can have a responsibility to provide care for a wide range of health needs, possibly including care for conditions not connected to the research question or study procedures. That responsibility, however, is significantly limited by the depth of the investigator's relationship with participants and the resource demands of providing such care.

In addition to ancillary care during a trial, there has also been a recent recognition that participants' needs for medical care may continue after the trial. International guidelines, such as the WMA's Declaration of Helsinki and reports by the U.S. National Bioethics Advisory Commission and the U.K. Nuffield Council, require that researchers consider the provision of post-trial care to participants after the research is completed. Spearheaded by the Office of AIDS Research (OAR), the NIH instituted a policy in 2005 requiring researchers in NIH funded HIV treatment trials to address the issue of post-trial access. We have explored whether and how this policy has been implemented by examining how approved international anti-retroviral protocols funded by the Division of AIDS address post-trial access (Shah et al 2009). We found that most protocols addressed post-trial access, more than 70% had specific mechanisms for post-trial access, but none guaranteed long-term sponsor funding after the trials. The plans reflected variation in local contexts and the uncertainty of predicting local conditions in the long term. Researchers primarily discharged their post-trial obligations by transitioning participants to external sources of care.

Previous work from the Department focused on practical and philosophical arguments related to post trial access (Grady 2005, Merritt and Grady 2006). The NIH policy suggests that the primary concern of many ethicists and activists has shifted from justifying an obligation to treat trial participants, to working out mechanisms through which treatment could be provided. Joseph Millum (2009) argues that this shift frequently conceals an important assumption: that if there is an obligation to supply treatment, then any party who could provide it may be prevailed upon to discharge the obligation. This assumption is false. The reasons why trial participants should get ART affect who has the duty to provide it. We should not burden governments with the obligations of sponsors, nor researchers with the obligations of the international community. And we should not deprive a group of treatment because their need is less salient than that of research participants. Insisting otherwise may lead to people being wrongfully deprived of access to antiretrovirals.

Obligations to trial communities: Fair Benefits, Reasonable Availability, and Responsiveness

Many commentators in the bioethics literature have assumed that for research in resource poor settings to be ethical, the products of the research must be made "reasonably available" to the host community. It is not completely clear what reasonable availability entails, but many have argued that research should only be conducted to test products that are expected to be useful in the country or community in which the research takes place. Others have required further that there should be a reasonable expectation that the intervention under study would be adopted in the local health care system if shown to be effective. In a series of papers published between 2002 and 2006, members of the Department with others argued that this represents a narrow view of the benefits of the research. Research can also benefit a country by providing health care, building research infrastructure, and by training researchers. We therefore proposed a framework for evaluating the benefits of research that goes beyond focusing simply on the availability of the intervention being investigated: the Fair Benefits Framework. According to this framework, it might, for example, be justifiable to approve a research project that will lead to vital capacity building for the host country but not to an intervention that addresses a disease that is a public health priority.

The Fair Benefits Framework has been subject to extensive commentary and criticism in the literature. Those who have been critical of the Fair Benefits Framework have argued that a specific research project can only be justified if the results of that research have some likelihood of being beneficial for the community in which it takes place. Members of the Department who accept the Fair Benefits Framework have argued that as long as trial participants and trial communities receive a fair amount of benefits, which does not have to include access to the intervention under study, there are no further obligations needed to avoid exploitation on those involved in the research. Wertheimer et al (2010) criticizes another attempt to develop an alternative to the fair benefits approach by arguing that this account of exploitation is not rooted in a more general account of fair transactions and that the author provides no argument for it.

Situating this debate in a broader context, Wolitz et al (2009) examines the concept of "responsiveness", widely endorsed by a number of international research ethics guidelines. Responsiveness is related to reasonable availability but requires that the research question address the health needs and/or health priorities of the host community. This paper argues that there is a lack of clarity in the concept of responsiveness and that the aims of responsiveness may not be served by making it an ethical requirement. It also argues that the goal of addressing the dearth of research on diseases of developing countries would be better achieved by mechanisms outside of the research context, such as public/private partnerships to incentivize high priority research.

Joseph Millum has argued that one can regard claims that research should provide certain types of benefits as attempts to rectify what is regarded as an unjust state of affairs. One example is the Convention on Biological Diversity, which has been signed by 191 countries. It sets standards for bio-prospecting, in which one attempts to develop indigenous genetic resources for commercial purposes, including the development of new drugs. One article of the Convention contains a requirement for benefit sharing between collaborating partners, including the country or group "owning" the resources. Although the principles in the Convention have been widely accepted, there has been little attempt to develop a comprehensive moral justification for the various claims, including the central claim that a group "owns" its genetic resources. Millum (2010) argues that we should understand the principles embodied in this declaration as instrumental in achieving distributive justice. Giving indigenous people at least property rights over the land they occupy would bring them closer to the situation they ought to

be in. Benefit sharing arrangements are one acknowledgement of these rights. Lie (2010) has provided a different sketch of an argument to the effect that claims about responsiveness should be seen as claims about obligations of researchers and research sponsors to shift the research focus towards poverty related diseases.

A couple of papers have discussed specific controversies in the literature. There has been a longstanding debate about the conflict between pharmaceutical patents and access to health care, in particular in resource poor settings. One recent example is the General Comment 17 from 2005 by the Committee on Economic, Social and Cultural rights which argues that the patent rights should always be subordinate to a right to health. Millum (2008) shows that this argument fails and that we cannot resolve the issue by appealing to existing human rights instruments. Rather, we need to situate the conflict in a broader framework of generally accepted moral values. The Bucharest Early Intervention Project was a randomized trial comparing institutional and foster care for abandoned children currently in institutions. Since it was carried out in a resource poor setting, it gave rise to criticism that the research exploited poor children in poor countries. Millum and Emanuel (2007) examines this claim, and argues that because the study responded to the health needs of the children in the study, and it was likely that the Romanian government would use the results of the study to improve care of abandoned children, that it therefore cannot be regarded as exploitative.

Educational Materials and Policy Discussions

The Department published an international research ethics case book in 2007 (Lavery et al 2007), describing a series of real, controversial cases, with commentaries from key individuals from around the globe, who were involved with or were knowledgeable about the issues raised by the case. The goal of the book was to move discuss of international research ethics past the controversy over the placebo-controlled trials of AZT to prevent mother-to-child HIV transmission and to expand awareness of the range of ethical issues that arise in international collaborative research. In addition to its use as a teaching tool, the book provides original ethical analyses of these cases.

In addition, department members have published textbook chapters (Lie 2007), reports of training courses (Lescano et al 2008), and policy related discussions (Lie 2007, Matsui and Lie 2007, Rid and Schmidt 2009).

Impact of Research: The Department's publications on the issue of ancillary care have been recognized as setting the agenda for research in this area. The proposal for a fair benefits framework been controversial, but is recognized as the point of departure for discussions of this topic, as reflected in a recent major article by Alex John London and Kevin J.S. Zollman in the Hastings Center Report. Departmental members are recognized as being the leading experts in the field of ethics of multinational research, as reflected in participation in international advisory bodies to WHO, UNAIDS, and the European Commission, as well as invitations to speak on this topic at major international meetings

Future Research Initiatives

Alan Wertheimer plans to explain and defend the use of procedural approaches in bioethics, in response to commentators criticizing fair benefits on the grounds that it is a purely procedural approach. He also plans a project that will explore what should be the motivation for an account of benefit-sharing in research—is it strictly to prevent the exploitation of communities, or are there other motivations?

Seema Shah plans to analyze how the responsiveness requirement can be reconceived to address the displacement effects of multinational research, to study whether international legal conflict can lead to ethical change in research ethics, to develop a better justification for post-trial obligations based on the responsible termination of the researcher-subject relationship, to compare fair benefits to responsiveness and other alternative proposals to avoid exploitation, and to help develop sound legal mechanisms for creating fair material transfer agreements in multinational research on stored samples.

Joseph Millum's future research will comprise three strands. First, further work in international research ethics. This will include completing projects on fair benefit sharing, a case study collection on the ethics of mental health research, an analysis of cultural barriers to the voluntariness of informed consent, and analyzing when and how background injustice should be factored into determinations of transactional fairness. Second, he will join Reidar Lie's project considering the ethics of priority setting in low- and middle-income countries. Third, he intends to work on issues in non-ideal theory that concern how researchers, clinicians, and foreign governments should act when a state is failing to secure health care for its citizens.

Reidar Lie will conduct a project on the ethics of research policy, examining questions such as obligations of countries to conduct research related to diseases of poverty and the role of implementation research. It will also involve developing a new methodology for priority setting. The project will be conducted through collaborating Ph.D. students in countries including China, Thailand and South Africa.

Dave Wendler will analyze the role that communities should play in the determination of whether research offers fair benefits. He will argue that community involvement is a necessary part of the fair benefits framework for several reasons, but that the important role the community plays does not turn fair benefits into a purely procedural account.

International Research Ethics Capacity Building

Department of Bioethics, Clinical Center, NIH

2007-2010

The Department's international capacity building efforts can be grouped into three categories: short, targeted training programs; long-term research capacity building; and policy and organizational advice.

Short, targeted training programs

Short training workshops

Continuing a previously established program of targeted ethics training, in the four year period from 2007 - 2010, the Department has conducted 25 2-3 day international ethics training workshops in 14 countries (see annex A for a list). While the Department has been responsible for the academic content of all of these workshops, all have involved local or international co-organizers, as well as sponsors. During this period approximately 1200 people were trained in the workshops. The target groups for the workshops have included biomedical researchers, research ethics committee members, Ministry of Health officials, and other policy makers in regions and countries where there is significant NIH funding for clinical research. NIAID funds have mainly covered the cost of travel for participants to attend the training workshops.

On-site training during the Clinical Center annual Ethics and Regulatory Aspects of Clinical Research course

Every year a number of participants from around the world follow the Ethical and Regulatory Aspects of Clinical Research course through videocasts. They register for the course, and there is a local person responsible for monitoring attendance. From 2004 to 2009, a total of 190 people from four international sites have followed the course. In addition, there are others who have followed the course, but not registered. In 2010, there are more than 10 remote sites registered, including sites in South Africa, Mexico and Sri Lanka.

Training IRB members

In the Fall of 2010, the Department began a new initiative in collaboration with the CNS IRB that gives international IRB members a chance to come to the Department for a three month period. Our first participants are from South Korea, one working in the Ministry of Health on clinical research regulations, and the other as a clinical trial coordinator at a major university. During this period they will follow the Ethics and Regulatory Aspects of Clinical Research course, sit in as observers in a number of the intramural NIH IRBs, and meet with staff from the Office of Human Subjects Research.

Long term research capacity building

Training of international experts in research ethics

The aim of this program is to train young bioethicists from outside the US to become international leaders in clinical research ethics. This is done through the following mechanisms:

1. Joint Ph.D. program with the University of Bergen
2. Establishment of a network of researchers primarily in East, South and South East Asia
3. Establishment of research collaboration with key bioethics centers
4. Visiting scholars at NIH

The aim of the joint Ph.D. program is is to recruit one student every second year. Three Ph.D. students have entered the program so far. See Annex B for more details.

International research collaborations

The Department has also initiated long-term research and educational collaborations with key institutions in Asia, Latin America and Africa. One aim of these collaborations is to initiate major studies on key issues in multinational clinical research, including proposals for reforming ethics review, comparative studies of the effects of different methods of obtaining informed consent, analysis of benefit arrangements for research, and attitudes and policy options for use of stored tissue samples. A second aim is to establish continuing programs in capacity development for research ethics. Annex B includes additional details.

Policy and organizational advice

International consultations

Members of the Department have worked with and served on national and international bodies, such as the European Commission and the World Health Organization. These efforts typically focus on advice in policy development. A recent consultation focused on the development of an international guidance document on treatment obligations to vaccine trial participants during and after a vaccine trial. The Department has provided advice on the development of research ethics guidelines in countries such as India and Sri Lanka, as well as the development of national standard operating procedures for IRBs in China.

Support to NIH international activities

Members of the Department have provided expertise and assistance to the NIH regarding development of policy and other training programs. For instance, members of the Department were instrumental in advising NIH on developing its policy for coverage of anti-retroviral drugs in HIV/AIDS trials. Members of the Department have served on—and even chaired —the study sections reviewing the bioethics grants for Fogarty International Center. Members of the Department have also helped organize and speak at international conferences held under the auspices of NIAID, the Fogarty International Center, and other NIH institutes. They have also worked with extramurally funded Fogarty bioethics grantees both at American universities and in

developing countries. The Department also provides a program of seminars for NIAID extramural program staff on current issues in research ethics.

Department of Bioethics-Fogarty International Center collaboration

Joseph Millum serves as a liaison between the Clinical Center Department of Bioethics and the Division of International Science Policy, Planning, and Evaluation at the Fogarty International Center (FIC). Millum is available for ethics consultation for Fogarty scientists, program officers, and grantees. He then consults with other faculty in the Department of Bioethics on more complex questions. He represents FIC in matters requiring ethics expertise. For example, he sits on the Trans-NIH Bioethics Committee, and is part of the steering committee of the Global Forum for Bioethics in Research. FIC is heavily involved in research ethics training in developing countries. Millum provides support to the program officer for the FIC bioethics training programs. He gives talks and teaches classes to the recipients of various FIC grants and their trainees, often in collaboration with other faculty or fellows from the Department of Bioethics. There is considerable interaction between the Department of Bioethics and FIC programs. For example, trainees from the Johns Hopkins-Fogarty African Bioethics Training Program visit the department several times during their stay at Johns Hopkins, in order to learn about the research in the department and to present their research proposals for critical feedback.

Department of Bioethics-DAIDS/NIAID collaboration

Reidar Lie and Seema Shah have worked to foster collaboration between the Department of Bioethics and NIAID/DAIDS in a number of ways. The service functions include ethics review of extramural research protocols for the Clinical Sciences Review Committee and the HIV Prevention Trials Network. Additionally, they arrange several applied ethics workshops each year on topics of special ethical interest, including research on the ethics of treatment interruption in research, research on orphans and wards of the state, and when experimental test results should be disclosed to participants. The workshops involve presentation of an ethical framework on an issue from a member of the Department of Bioethics, presentation by a DAIDS medical officer of a case that has arisen in DAIDS that raises these ethical issues, and facilitated discussion about the case in light of the relevant ethical principles. Finally, members of the Department of Bioethics are available to provide ethics consultation for the Division of AIDS. In the past, we have provided ethics consultation on complex and unsettled ethical issues related to ongoing research, including issues related to obligations to subjects in other trials and how to balance conflicting clinical care obligations with research obligations. Some of these consultations have stimulated further research and publication on the issues involved.

ANNEX A. International Capacity Building Workshops., 2007 – 2010 only. Prior list available on request

2007

Beijing, China, June 2007

Nagasaki, Japan, July 2007

Kathmandu, Nepal, August 2007

Bamako, Mali, December 2007

2008

Jeonju, Korea, March 2008

Hanoi, Vietnam, June 2008

Tokyo, Japan, June 2008

Nagasaki, Japan, July 2008

Bangkok, Thailand, August 2008

2009

Ho Chi Min City, Vietnam, April 2009

Manila, Philippines, April 2009

Singapore, April 2009

Nagasaki, Japan, July 2009

Bangkok, Thailand, August 2009

Lima, Peru, August 2009

Cusco, Peru, August 2009

Bandung, Indonesia, September 2009

Kuala Lumpur, Malaysia, November 2009

Istanbul, Turkey, December 2009

2010

Kyoto, Japan, January 2010

Nagasaki, Japan, June 2010

Jakarta, Indonesia, July 2010

Bandung, Indonesia, July 2010

Manila, Philippines, August 2010

Lusaka, Zambia, August 2010

ANNEX B International collaborating institutions

The Department collaborates with the University of Bergen, Norway, in a joint Ph.D. program. Students from developing countries are admitted to Bergen Ph.D. program in bioethics. They are funded for the first two years by the Norwegian government and take coursework in Bergen. Upon successful completion of this coursework, they transfer to the Department of Bioethics for their final two years with funding from the Department. Three students have entered the program

Allen Alvarez, University of the Philippines, completed Ph.D. in 2009

Nicola Barsdorf, University of KwaZuluNatal, entered the program in 2007, currently at NIH

Chunshui Wang, Peking Union Medical College, entered the program in 2009, currently at Bergen

In addition, there is an ongoing collaboration with Bergen University to strengthen capacity in ethics in the Department of Philosophy, Makerere University, Uganda. One junior faculty member, John Barugahare, has entered the Bergen Ph.D. program in Philosophy, with funding from Bergen, in a collaborative arrangement with the Department.

The collaboration in the Ph.D. program is part of a more comprehensive attempt to strengthen research capacity in bioethics in key international institutions. These include

- University of KwaZulu Natal, South Africa
- University of Tokyo, Japan
- NAMRID, Peru
- Chulalongkorn University, Thailand
- Peking Union Medical College, China
- University of the Philippines, Manila, Philippines
- Makerere University, Uganda

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